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Volume 11 **Neurology** *Number 7*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

JULY 1961 • *Contents*

Neurologic Sequelae of Japanese B Encephalitis 553
LT. RALPH W. RICHTER, M.C., U.S.N.R., and
LT. SADATOMO SHIMOJYO, M.C., Japanese Navy

An Exfoliative Cytologic Study of Intracranial Fluids 560
BERNARD NAYLOR, M.S., M.B., Ch.B.

Multiple Endocrine Adenomas (Lloyd's Syndrome) and Psychomotor Epilepsy 571
W. KRAMER, M.D., and B. MAKKINK, M.D.

Beta-Glucuronidase Activities in Tumors of the Nervous System 578
NORMAN ALLEN, M.D.

A Brain Stem Lesion of Unusual Etiology: A Case Report 597
CAPT. H. RICHARD McFARLAND, M.C., U.S.A., and
MAJ. B. LIONEL TRUSCOTT, M.C., U.S.A.

Use of Anticoagulants in Patients with Progressive Cerebral Infarction 601
ALAN BARHAM CARTER, M.D., F.R.C.P., D.P.M.

A New Method for Graphic Study of Human Movements 610
GUILLERMO DIERSSEN, M.D., MARY LORENC, and ROSE MARIE SPITALERI

(Continued on following page)

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Contents—*Continued*

Acute Inclusion Encephalitis of Herpes Simplex Type 619
CARL B. BOOTH, M.D., HAURO OKAZAKI, M.D., and J. CLAUDE GAULIN, M.D.

Water Intoxication Following Intracranial Surgery 630
ROBERT L. McLAURIN, M.D., LIONEL R. KING, M.D., HARVEY KNOWLES, JR., M.D., and EUGENE B. ELAM, M.D.

A Syndrome Clinically Resembling Amyotrophic Lateral Sclerosis Following Chronic Mercurialism 639
ARTIN K. KANTARJIAN, M.D.

Spinal Leptomeningeal ("Pial") Lipoma: A Case Report 645
O. RHETT TALBERT, M.D., and C. N. SIMMONS, M.D.

Book Reviews 649

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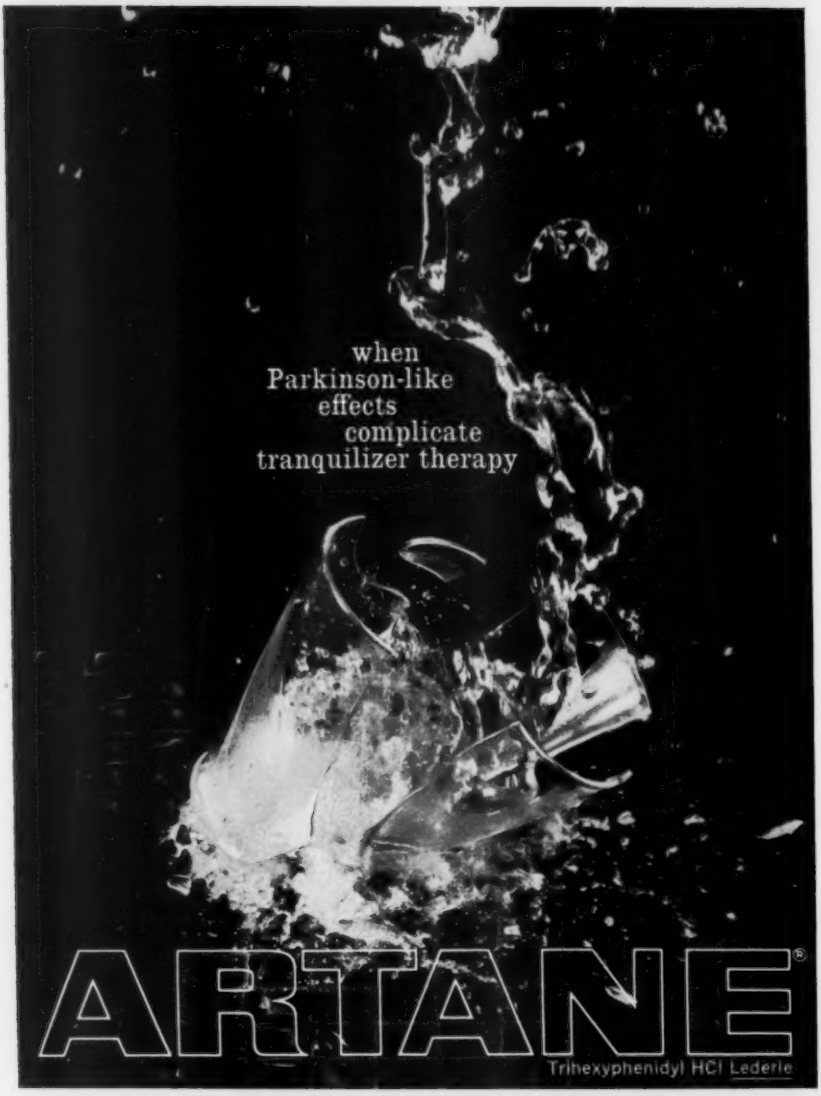

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Neurology Volume 11 • Number 7

Neurologic sequelae of Japanese B encephalitis

Lt. Ralph W. Richter, M. C., U.S.N.R., and

Lt. Sadatomo Shimojyo, M. C., Japanese Navy

JAPANESE B ENCEPHALITIS, caused by an arthropod-borne virus, has been found to occur in almost all of eastern Asia[1–6] including Japan, eastern Siberia, China, Okinawa, Korea, Formosa, Guam, Philippine Islands, Viet Nam, Malaya, and southeastern India. Permanent sequelae are not uncommon in those surviving a severe attack. This paper presents case histories of U.S. Marines severely infected on Okinawa during 1958 in order to illustrate the variability of neurologic residuals. Statistics of recent epidemics in Japan and reports of characteristic sequelae are also reviewed.

During 1958, there were 16 cases of Japanese B encephalitis among American military personnel on Okinawa, of which 8 occurred among U.S. Marine Corps enlisted men. Of the 8 marines, 4 had mild to moderately severe acute illnesses lasting approximately one week, with symptoms including fever, headaches, stiff neck, vomiting, and lethargy; 2 of the men had generalized seizures on the second day of illness. Initial cerebrospinal fluid examinations demonstrated between 300 and 600 white blood cells, predominantly lymphocytes, per cubic millimeter. These 4 men recovered completely and returned to duty within one month. Diagnostically significant rises in the hemagglutination inhibition titers for Japanese B virus were reported in all cases by the 406th U.S. Army Medical Laboratory.

The following 4 case descriptions (Table 1) are of the marines who suffered severe infections.

Case 1. (R. D. W.) This 20-year-old private was stuporous, disoriented, and combative during the first week while febrile. Three weeks after onset, he seemed severely retarded. Masked face, rigid gait with festination, cogwheel rigidity, and tremor of the left arm and leg were noted. The neurologic signs cleared in about ten weeks, but moderate intellectual

From the Neurology Branch of the Neuropsychiatric Service, U. S. Naval Hospital, Oakland, Calif.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large.

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Read at the twelfth annual meeting of the American Academy of Neurology, Miami, April 28, 1960.

TABLE 1

JAPANESE B ENCEPHALITIS AMONG U. S. MARINE CORPS PERSONNEL, OKINAWA, 1958

Patient	Age	Sex	Date of onset	Date of sera	Titer*	Spinal fluid	Characteristics of acute phase	Outcome
R.D.W.	20	Male	Sept. 10	Sept. 13 Oct. 1	1: 640 1: 320	830 cells 60% lymphocytes	Stuporous for one week. Tremor, masked face, cogwheel rigidity, and mental change at three weeks	Sequelae: Impaired memory and judgment, impulsiveness, concretism
F.D.S.	21	Male	Oct. 24	Oct. 27 Nov. 17	<1: 10 1: 320	390 cells 70% lymphocytes	Semicoma for 11 days. Focal right-sided seizures	Sequelae: Psychosis, mental deficiency, cerebral atrophy
J.F.C.	21	Male	June 5	June 10 June 30	1: 80 1:1,280	505 cells 60% lymphocytes	Nine days' coma. Quadriparesis and mutism at 3 months	Sequelae: Psychosis, mental deficiency, left hemiparesis, spasticity, Babinski
R.A.B.	21	Male	Sept. 21	Oct. 1 Oct. 9	1: 80 >1:5,120	366 cells 53% lymphocytes 47% polymorphs	Admission: Headache, stiff neck, fever (103°). Confusion for 2 days, then coma for 9 days until death	Death

*Hemagglutination inhibition titer

deficits persisted along with restless, negativistic, and assaultive behavior. He was retired from active duty with disability five months later. Organic mental disturbances were manifested by impaired capacity for reasoning and judgment and memory and intellectual defects. Marked personality changes were still present eighteen months after infection, and outbursts of antisocial behavior have led to his recent imprisonment.

Case 2. (F. D. S.) This 21-year-old private was febrile and semicomatose for eleven days. Right-sided focal seizures occurred. He was first capable of walking three weeks after onset. Two months later, the neurologic examination was normal, but psychologic testing revealed that he functioned at a mentally deficient level. Nine months after infection, he became severely psychotic. Widespread personality disorganization was evident, and the IQ functioning was 77 compared with an enlistment equivalent of 119. He wandered aimlessly, hallucinated, and was so inappropriate in behavior and assaultive that he needed locked ward supervision and heavy sedation. A pneumoencephalogram revealed moderate dilation of the entire ventricular system. Seventeen months after infection, he was first allowed custodial home leave. The mental deficit and organic psychosis persisted.

Case 3. (J. F. C.) Four days after onset of fever and myalgias, this 21-year-old corporal was comatose when admitted to the hospital. Temperature was 105.4° F., and severe nuchal rigidity was present. Spinal fluid showed 505 cells per cubic millimeter, 60% of which were lymphocytes. For nine days, he continued in coma with temperatures between 101 and 103° F. Numerous generalized seizures occurred. A tracheostomy was performed, and periodic use of a respirator was necessary. Thirteen days after onset, he first seemed aware of his surroundings and responded to his name. By the twenty-sixth day, the hemagglutination inhibition titer had risen to 1:1,280. He made only slow progress and suffered from quadriparesis, muscle wasting, mental retardation, mutism, and incontinence. Three months later, he first was able to walk with the help of parallel bars. Eight months after infection, psychologic testing revealed him to be functioning at a mentally defective level with an IQ equivalent of 65. Fifteen months after infection, left hemiparesis with spasticity, hyperreflexia, and Babinski sign were still found along with anisocoria, dysarthria, inappropriateness, and defective intelligence. Twenty-one months after infection, he was at home but could not be trusted to remain alone because of such unpredictable behavior as cutting screens with a pocket knife. He cannot engage in conversation or take care of his personal habits.

Case 4. (R. A. B.) This 21-year-old private had headache, stiff neck, fever, chills, and vomiting on the day before admission. When hospitalized, he was markedly confused. Temperature was 105° F., and severe nuchal rigidity was present. On the third day he lapsed into coma. Pupils became dilated and fixed. Bilateral Babinski signs were present. In spite of intensive care, including use of a respirator and intravenous hydrocortisone, he died on the eleventh day after onset of illness. By the time of death, the hemagglutination inhibition titer was greater than 1:5,120. The pathology in this case* was similar to that seen in other cases described by Haymaker and Sabin,[7] Zimmerman,[8] and Suma.[9] Focal as well as widespread destruction of ganglion cells in the cerebral cortex, basal ganglia, thalamus, substantia nigra, red nucleus, cerebellar cortex, and gray matter of the spinal cord are characteristically present. Intense perivascular infiltration of lymphocytes and mononuclear cells was present in affected areas.

*The neuropathologic study in this case was made by Maj. Joseph F. Metzger, M. C., U. S. A., at the U. S. Army Hospital, Ryukyu Islands, and was reviewed by Dr. Webb Haymaker at the Armed Forces Institute of Pathology, Washington, D. C.

DISCUSSION

The serious menace of Japanese B encephalitis is most apparent in Japan, where, in summer and fall epidemics from 1948 to 1959, 36,871 cases with 15,391 deaths were reported. The yearly variations of clinically apparent infections and deaths are illustrated in Figure 1. Serologic surveys of the population indicate that there may be several hundred inapparent infections for every case severe enough to be reported.[10] The high mortality rate should be further qualified by the fact that many of the cases occurred in rural areas where full medical supportive therapy was lacking. Even with optimum treatment, the outlook is poor. Between 1948 and 1954, Dr. M. Yokota[11,12] helped to treat 1,592 serologically verified cases of Japanese B encephalitis at the Koma-

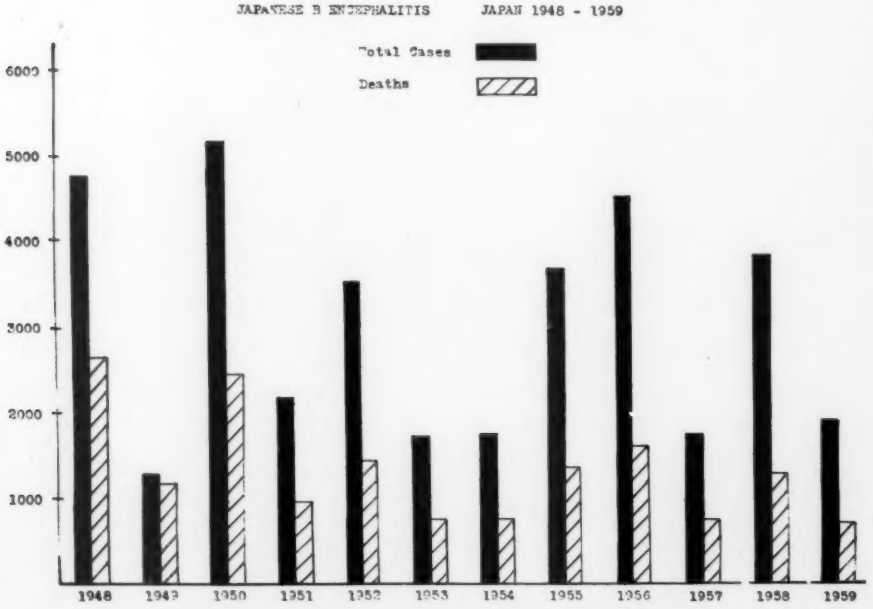

Fig. 1. The yearly variations between 1948 to 1959 in Japan of reported cases and deaths from Japanese B encephalitis. Total cases, 36,871. Deaths, 15,391

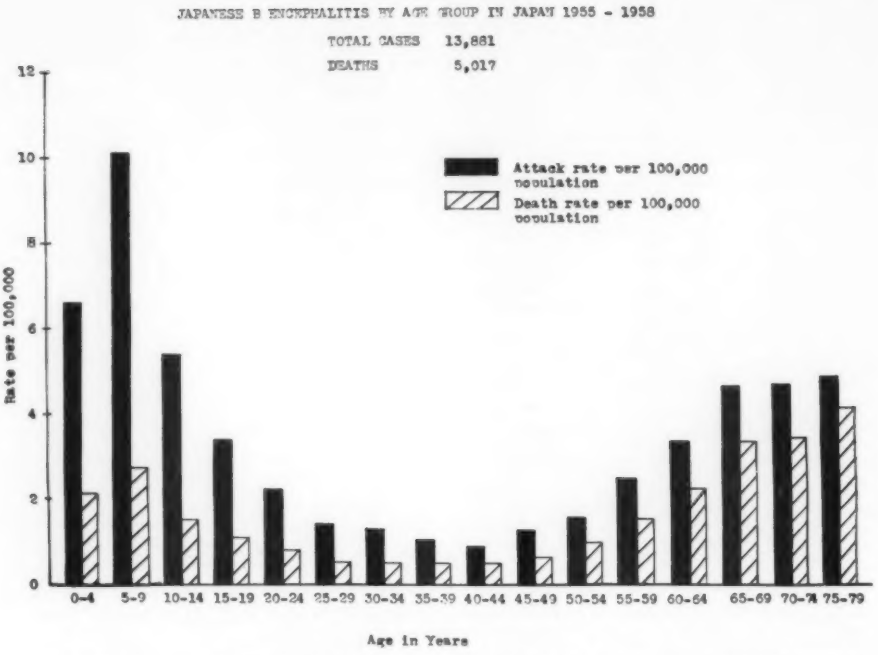

Fig. 2. The Japanese B encephalitis attack rate and death rate by age group per 100,000 population in Japan between 1955 and 1958

gome Contagious Hospital in Tokyo. The mortality rate was 22.9%, and 18.2% of the patients had neurologic sequelae when examined one month after infection.

The attack rate and death rate by age group per 100,000 population in Japan between 1955 and 1958 are depicted in Figure 2. The attack rate is highest above the age of 65 and below the age of 15 years. Infections below the age of 1 year are extremely rare. Between 1946 and 1959, Yokota observed only 18 cases in children below the age of 1 year. Widespread subclinical infections producing a passively acquired immunity in the newborn may account for the low (approximately 1%) incidence of infection below 1 year of age which is seen in Japanese B encephalitis and also in St. Louis encephalitis.[13] This is in contrast to Western equine encephalitis; in California from 1945 to 1953, 26.3% of those infected were below 1 year of age.[13]

Dr. Akio Goto[14] has permitted us to include some of his five-year follow-up observations on patients who were hospitalized at the Komagome Contagious Hospital and the Toyotama Hospital in Tokyo during the epidemic of 1948. Of 690 patients initially seen, 163 died during the acute infection. The 143 patients (115 children) with sequelae one month after infection were followed over a five-year period, at the end of which time 4 (3 children) were dead, 31 (23 children) had recovered, and 108 (89 children) still demonstrated sequelae. Neurologic sequelae were noted in 68 cases (56 children). Psychiatric sequelae were seen in 98 cases (79 children), and mental deficiency was present in 73 cases (62 children). Combinations of neurologic, psychiatric, and intelligence disorders were frequently seen, especially among affected children.

The nature of the neurologic deficits described by Dr. Goto after five years is outlined in Tables 2 and 3. Motor disorders, speech disturbances, and cranial nerve ab-

normalities were observed. Of considerable interest were the 8 patients, 6 of whom were below the age of 35 years, who demonstrated features of a Parkinson syndrome; 1 was a 43-year-old woman whose symptoms began during the acute infection and who five years later had improved but still had masked facies, hyperhidrosis, slow monotonous speech, cogwheel rigidity, and rest tremor involving the left arm and leg. Parkinson symptoms as long-term sequelae are rarely reported. Dickerson, Newton, and Hansen[15] have noted that, during the acute phase of illness, symptoms of masked face, slow thick speech, rigidity, and tremor are common, but, in this series, most of these symptoms cleared by the tenth week. A marine (Case 1) in our series had parkinsonian symptoms which disappeared after ten weeks. These symptoms may follow soon after an acute attack of Japanese B encephalitis, but these signs are usually mild and tend to slowly disappear or remain stable. The progressive parkinsonism seen after von Economo's encephalitis is highly atypical for Japanese B encephalitis.[14]

Convulsive disorders were observed by Goto in 4 children; 1 was a 6-year-old girl who began to have generalized convulsions at the time of infection and continued to have intermittent seizures until her death in status epilepticus. Another was also 6 years old at the time of infection and had sequelae of right hemiplegia, dysarthria, and mental retardation. Generalized seizures with right-sided focal onset began six months after infection. In spite of therapy with phenobarbital, Dilantin, and Phenurone, she still continued to have 2 to 3 seizures a week. Yamamoto,[16] who observed convulsive disorders as sequelae in 5 out of 77 cases, believes that convulsions during the acute stage of illness are a poor prognostic sign and are seen more commonly in those who have sequelae. The marines (Cases 2 and 3) who now have severe residuals ex-

TABLE 2

NEUROLOGIC SEQUELAE IN 68 PATIENTS FIVE YEARS AFTER ACUTE INFECTION

Number	*Defects*
	Muscle tone disorder
41	Spasticity
3	Hypotonicity
	Motor paralysis
13	Hemiplegia
10	Monoplegia
2	Quadriplegia
	Reflex abnormalities
22	Hyperreflexia
7	Ankle clonus, sustained
	Pathologic reflexes
5	Babinski
1	Oppenheim
1	Rossolimo
	Primitive reflexes
8	Grasp
6	Snout reflex
2	*Sensory disorder*
	Speech disorders
2	Global aphasia
1	Partial aphasia
19	Dysarthria
7	Parkinson-like weak monotone

TABLE 3

NEUROLOGIC SEQUELAE IN 68 PATIENTS FIVE YEARS AFTER ACUTE INFECTION

Number	*Defects*
	Cranial nerve abnormalities
2	Anisocoria
4	Irregular pupils
1	Mydriasis
3	Light reflex impairment
2	Convergence paralysis
1	Conjugate deviation of eyes
2	Ptosis
1	Nystagmus, sustained
5	Facial palsy
1	Hypoglossal palsy
11	Masked facies
	Autonomic disorders
3	Excessive salivation
3	Hyperhidrosis
1	Hypertrichosis
1	Propulsive gait
21	Adiadochokinesia
7	Tremor
7	Chorea, tics, athetosis
8	Parkinson's syndrome
4	Convulsive disorders

TABLE 4

MENTAL DEFICIENCY AS SEQUELAE OF JAPANESE B ENCEPHALITIS IN 73 CASES AFTER FIVE YEARS
(Binet Modified IQ)

Age in years at acute infection	0–5	6–10	11–20	21–30	31–40	40 and over
Severe defect (IQ 0–20)	2	2				
Moderate defect (IQ 20–50)	15	10	1			
Mild defect (IQ 50–70)	14	13	7	4	3	2

perienced generalized and focal seizures during the acute illness. In contrast, 2 of the marines with mild infections experienced generalized seizures but did not have sequelae. Seizure disorders as late sequelae are probably rare.

The degree of mental deficiency in 73 cases, according to age group, which were examined by Goto five years after infection is listed in Table 4. The youngest of the children, especially those below 5 years of age, tended to have the greatest intellectual impairment and also frequently exhibited neurologic deficits. Some of the older children showed signs of slowly improving mental function. Many of the children with organic mental deficits also had psychiatric disturbances characterized by emotional instability, restless overactivity, and agitated, antagonistic, and assaultive behavior. Adults usually demonstrated only mild intellectual defects, particularly in the realm of abstract conceptual thinking. Some also showed the type of psychiatric disturbance which accompanied the moderate organic mental deficit in 1 of our marines (Case 1). Severe intellectual deterioration such as seen in 2 of the marines (Cases 2 and 3) was rare in adults. This observation corresponds to that of Weaver,[17] who found that, in a group of 108 American military personnel who had psychologic studies after infection in 1950, only 5 patients had organic mental sequelae severe enough to warrant separation from service.

The prevention of sequelae is dependent on achieving effective control of the disease. In spite of intensive investigation into the epidemiology of the disease in many endemic areas, there are still gaps in our knowledge of the part which mosquitoes or other arthopods, mammals, wild birds, and man play in the spread of infection. In Japan, Culex tritaeniorhynchus has been found to be the mosquito species most commonly infected in nature by the Japanese B virus, yet evidence that this mosquito as a natural vector actually transmits the virus to natural hosts such as chicks, pigs, egrets, and black-crowned night herons has only recently been conclusively demonstrated.[18] The role of nestling wild birds, especially of the heron family, in rapid seeding of vector populations in Japan is well known.[19] Although epidemics of encephalitis have been occurring among horses,[3] and serologic surveys have shown a high antibody incidence in the blood of such domestic animals as pigs, goats, dogs, cattle, and sheep,[2,3] it is unlikely that man and domestic animals play an important role in virus dissemination. Attempts have been made to control the disease by the use of vaccines prepared from formalinized mouse brain and from chick embryo. In spite of widespread vaccinations, unmodified severe infections have still occurred among some of those vaccinated.[20] American military personnel are no longer being vaccinated against Japanese B virus. Efforts directed towards the development of a more effective vaccine have as yet been unsuccessful.

SUMMARY

The cases of 4 marines who sustained severe attacks of Japanese B encephalitis on Okinawa are presented; 1 died, and the other 3 men have permanent neurologic sequelae, among which are mental deterioration, psychosis, cerebral atrophy, speech disturbance, and hemiparesis.

Recent epidemics in Japan are reviewed along with the reported characteristic sequelae. The combination of neurologic impairment and mental deterioration was common, especially among the youngest infected children.

Effective control of this disease has not yet been achieved.

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An exfoliative cytologic study of intracranial fluids

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WHEREAS TWENTY YEARS AGO the use of diagnostic exfoliative cytology was exceptional, today in North America it is commonplace. This branch of pathology finds its most widespread application in investigation of the respiratory and female genital systems; utilization of the method in the diagnosis of lesions of the central nervous system has received relatively scant attention. However, a perusal of the literature shows that, since the beginning of this century, there have been about 60 publications which mention specific instances of finding tumor cells in either intracranial or intraspinal fluids. This does not take into account tumors of the malignant lymphoma and leukemia groups. The great majority of authors have reported finding tumor cells in cerebrospinal fluid obtained by lumbar puncture; fewer mention finding tumor cells in fluids obtained directly from the cranial cavity. The impression given in many instances is that the identification of tumor cells in a fluid derived from the central nervous system has been a unique or most uncommon experience for the authors concerned. But one is also left with the impression that tumor cells would be found more frequently in these fluids if suitable technics were used to demonstrate them and if persons seeing them could, with assurance, recognize them for what they are.

Intracranial fluids (usually ventricular fluids) are often withdrawn from patients who are obscure diagnostic problems, who are suspected of having brain tumor, or who are undergoing craniotomy. In many instances, the cerebrospinal fluid withdrawn from a lateral ventricle is the first specimen of such fluid obtained; this applies particularly to brain tumor suspects. In view of these facts and of the relatively few reports of finding tumor cells in intracranial fluid, a series of such fluids has been examined by conventional methods of exfoliative cytology. The aim has been to determine how frequently and how easily tumor cells can be found, whether the exfoliated cells of gliomas can be distinguished from those of metastatic epithelial neoplasms, and whether the finding of tumor cells in these fluids can be of diagnostic value. This study has been concerned entirely with qualitative cytology. Total and differential cell counts of these fluids are superfluous in the search for tumor cells; the diagnosis of neoplasm is the same whether tumor cells are scanty or in abundance. Likewise, biochemical examinations of the fluids have been omitted, for biochemical abnormalities in themselves are not diagnostic of neoplasm.

PREVIOUS REPORTS

In Table 1 are listed 38 reported cases in which the finding of tumor cells in intracranial fluid has been described.[1–9] In accordance with the policy of Spriggs,[10] who reviewed the literature, reports have not been excluded which do not illustrate the tumor cells; in such cases, reliance has to be placed on the description of the cells and the clinical and pathologic pictures.

The illustration of the cells of Case 5 of Platt[3] does leave some doubt as to whether they are malignant; however, this case has not been excluded because of this.

It is quite possible that the specimen of cerebrospinal fluid which contained cells of

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cerebellar spongioblastoma, described by Ostertag,[11,12] was obtained from within the cranium. He does not make this clear, and so this case has not been included.

The single case of Emanuel[13] has been excluded. The neoplasm was a meningioma, a rather unlikely contributor of tumor cells to the cerebrospinal fluid, and there was some debate as to whether the cells were actually those of the neoplasm.

Spriggs[10] excluded the first 11 of Forster's[1] 12 cases on account of the unconvincing cytologic data. In 9 of these 11 cases, tumor cells were said to be demonstrated in intracranial fluid. The photographic evidence in Case 5 is acceptable, and this example has been included in Table 1.

MATERIAL AND METHODS

During a two-year period, 76 intracranial fluids were received from the Neurosurgical Service of The University of Michigan Medical

TABLE 1

TUMOR CELLS IN INTRACRANIAL FLUIDS: PREVIOUS REPORTS

Source of fluid	*Author*		*Type of neoplasm and remarks*
Lateral ventricle	Forster[1]	(Case 5)	Glioma of cerebrum (photograph and drawing)
	Schroeder and associates[2]	(Case 2)	Glioma of cerebellum (photograph)
		(Case 3)	Bronchogenic carcinoma (photograph)
	Platt[3]	(Case 5)	Glioblastoma multiforme (photograph)
		(Case 11)	Glioblastoma multiforme (photograph)
	Chesterman and Semple[4]		Adenocarcinoma of stomach
	Daum and Gruner[5]	(Case 2)	Lymphosarcoma
		(Case 3)	Adenocarcinoma; primary unknown
		(Case 4)	Malignant melanoblastoma of skin
		(Case 5)	Adenocarcinoma of stomach
	Sayk and Lemke[6]	(Case 2)	Glioblastoma multiforme (photograph)
	McMenemey and Cumings[7]	(Case 1)	Astrocytoma, grade IV (photograph)
		(Case 2)	Oligodendroglioma
		(Case 6)	Bronchogenic "squamoid" carcinoma (photograph)
		(Case 8)	Carcinoma; primary unknown (photograph) Cells look like adenocarcinoma
		(Case 11)	Malignant melanoblastoma of skin (photograph)
		(Case 12)	Chordoma (photograph)
	Marks and Marrack[8]	(Case 1)	Medulloblastoma. No histologic confirmation
		(Case 9)	Bronchogenic carcinoma
		(Case 10)	Primary meningeal melanomatosis (photograph)
		(Case 11)	Astrocytoma
		(Case 12)	Adenocarcinoma of stomach (photograph)
		(Case 13)	Bronchogenic carcinoma
		(Case 14)	Astrocytoma
		(Case 15)	Suprasellar mass. No histologic confirmation
		(Case 16)	Malignant melanoblastoma of eye (photograph)
		(Case 17)	Suprasellar mass. No histologic confirmation
Cisterna magna	Danisch and Nedelmann[9]		Malignant thymoma
	Forster[1]	(Case 5)	Cerebral glioma (photograph and drawing)
	Platt[3]	(Case 6)	Medulloblastoma or cerebellar sarcoma (photograph)
	McMenemey and Cumings[7]	(Case 10)	Hilar mass, presumably carcinoma
Cerebral cyst	Forster[1]	(Case 5)	Cerebral glioma (photograph and drawing)
	Schroeder and associates[2]	(Case 3)	Bronchogenic carcinoma (photograph)
	Platt[3]	(Case 9)	Astrocytoma (photograph)
		(Case 10)	Oligodendroglioma (photograph)
		(Case 11)	Glioblastoma multiforme (photograph)
Parapituitary cyst	Platt[3]	(Case 12)	Cyst of Rathke's pouch (photograph)
Leaking craniotomy wound	Schroeder and associates[2]	(Case 3)	Bronchogenic carcinoma

Center. The surgeons were encouraged to submit any fluid obtained from within the cranium regardless of whether the patient was suspected of having an intracranial neoplasm. The total number of specimens received by no means represents the number of fluids withdrawn from the cranium during the two-year period but is more a reflection of the vicissitudes of procuring research material in a large general hospital.

Specimens were sent as soon as possible to the Pathology Department and were examined immediately. The 2 methods used were the serum-toluidine blue wet film advocated by McCormack and colleagues[14] and the wet-fixed smear stained by Papanicolaou's method. The wet-film method proved to be interesting and useful in this investigation. It gave us some rapid diagnoses and, on a few occasions, enabled us to anticipate the need to prepare more smears than usual for the Papanicolaou stain. Comparing the approximate number of cells seen on the wet film with those on the permanent preparation made us realize that the loss of cells from the slide in preparing the latter is negligible. Occasionally, small tumor cells have been overlooked or misidentified in the over-all blueness of the wet film, especially when protein precipitation was heavy or there was much debris in the sediment of the specimen. Rather than separate the slide and coverslip for subsequent Papanicolaou stain, it was more convenient to discard the wet film and prepare smears anew for the Papanicolaou stain.

The Papanicolaou stain has not been used generally in this type of cytology; Platt[8] was apparently the only one who used it exclusively. Spriggs[10] stated that the Papanicolaou method as applied to cerebrospinal fluid was not very satisfactory, and McMenemey and Cumings[7] found that, in their hands, Leishman's stain gave better results than Papanicolaou's. We have used only the Papanicolaou method for the permanent preparations and find it most satisfactory. In this laboratory, thousands of routine cytologic specimens of all types were processed by the Papanicolaou method annually, and no doubt familiarity with the one method has brought about reliance on it to the exclusion of others.

The details of the method are as follows:

As much fluid as possible is centrifuged at about 2,000 rpm in a conical tube for about five minutes; all the supernatant is poured off by completely inverting the tube. There is enough residual fluid adherent to the inside of the tube to allow a very small volume to recollect over the sediment when the tube is reinverted—enough to provide a vehicle for the cells in the wet film and several permanent smears.

Wet-film method. After the deposit (which may be invisible to the naked eye) is stirred with a loop, a loopful is put on a slide; 1 drop of the serum-toluidine blue stain is added to it, and both are mixed with a corner of a coverslip. The same coverslip is then placed on the mixture which is usually ready to be examined immediately; occasionally, one may have to wait a minute or two until the stain penetrates the cells. This preparation is discarded after it has been examined.

Papanicolaou stain. After the wet film has been made, 2 loopfuls of the sediment are put on a slide; these are quickly spread in a longitudinal and crisscross manner with the loop, over an area about 3 by 2cm., and the smear is immediately immersed in 95% ethyl alcohol. After one minute in the alcohol, the smears may be stained by Papanicolaou's method, or they may be kept in the fixative for several days before staining.

Usually, we prepare 3 smears for the Papanicolaou stain. They are immersed in the same jar of fixative and are kept separate from each other by having a paper clip attached to one end of each slide. Important points in the preparation of these smears are the following: They should be immersed in the fixative immediately after they have been made, before the slightest trace of drying, and the immersion must be smooth and swift; otherwise, "ribbing" of the smeared material is liable to occur. The slides need not be "chemically" clean. If the sediment is not visible to the naked eye or if the fluid is clear, we have taken the precaution of albuminizing the slides before the smears are made. For this, Mayer's albumin fixative is lightly smeared over the slide before the sediment is put on. Generally, we prefer to do without the albumin because it gives a slightly colored background under the microscope and some-

times slightly interferes with the clarity of the staining. The mixture remaining in the centrifuge tube is kept in the refrigerator in case there is need to prepare more smears. We have made perfectly satisfactory smears from this stock up to two days after its collection.

The systematic screening of only one smear is usually all that is necessary. When tumor cells are present, they are usually easily found and identified as such, since the number of cell types likely to be encountered in these fluids is relatively small.

RESULTS

In all, 76 intracranial fluids, collected by trephination or craniotomy, were examined; 46 specimens were from cases of intracranial neoplasm, 34 malignant and 12 nonmalignant, and 30 of the specimens were from cases in which no intracranial neoplasm was detected. Table 2 lists the various sources of the fluids and the number which contained tumor cells. An account of these cases in which tumor cells were found will be given, as well as 1 case of porencephalic cyst from which characteristic lining cells were recovered.

Cerebrospinal fluid from the lateral ventricles was submitted from 8 cases of metastatic intracranial neoplasm; tumor cells were seen in 3 specimens.

Case 1. *Metastatic malignant melanoblastoma.* A man, age 63 years, was admitted to hospital on December 12, 1958, on account of a six-month history of inattentiveness, headache, and grand mal seizures. He was lethargic, and there was a questionable left hemiparesis but no papilledema. A 2 x 1 cm. subcutaneous whitish nodule was found on the mediodorsal aspect of the left foot.

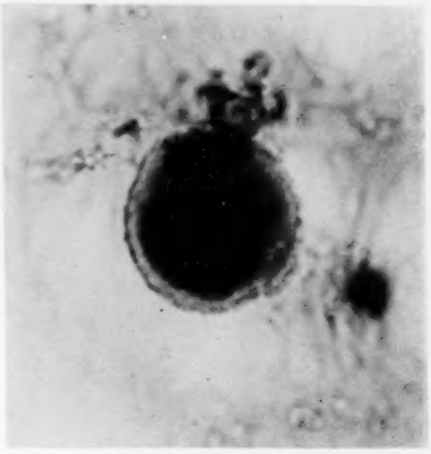

Fig. 1. Ventricular cerebrospinal fluid. Cell of metastatic malignant melanoblastoma against a background of hemolysed blood. The cell boundary is well defined, and cytoplasm is not scanty. No pigment seen in this cell. Papanicolaou stain. × 1,480

In 1945, he had an invasive malignant melanoblastoma of the skin excised from the dorsum of his left foot.

A chest roentgenogram showed a hilar mass; carotid arteriograms and ventriculograms were inconclusive. The only abnormality of his spinal fluid was the presence of 13 "mononuclears" per cubic millimeter. The patient died on December 28, 1958.

The ventricular fluid obtained before death contained cancer cells (Fig. 1). They were round, about 15 μ in diameter, and had relatively large, hyperchromatic, central or slightly eccentric nuclei. They were reported as cancer cells, and the

TABLE 2

SOURCES OF FLUIDS: TUMOR CELL RECOVERY

Source of fluid	*Number of specimens*	*Number with no intracranial neoplasm detected*	*Benign intracranial neoplasm**		*Malignant intracranial neoplasm*	
			Number of cases	*Tumor cells recovered*	*Number of cases*	*Tumor cells recovered*
Lateral ventricle	66	25	10	0	31	5
Cisterna magna	2	1	0	0	1	1
Cerebral cyst	6	4	0	0	2	2
Cerebellar cyst	1	0	1	0	0	0
Pituitary cyst	1	0	1	1	0	0
Totals	76	30	12	1	34	8

*These were 4 craniopharyngiomas, 3 acoustic neurilemmomas, 2 cerebellar hemangioblastomas, 1 pituitary adenoma, 1 meningioma, and 1 spinal neurilemmoma.

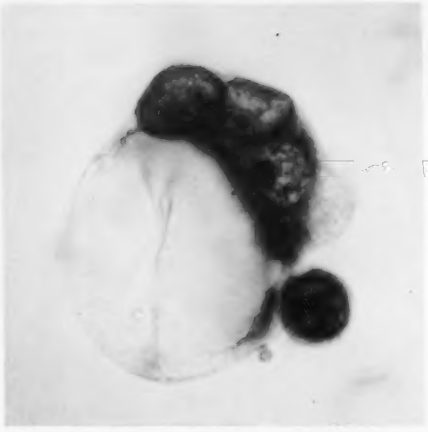

Fig. 2. Ventricular cerebrospinal fluid. Metastatic bronchiolar cell carcinoma cells, one large and one small. The former is a classic adenocarcinoma cell with a distinct boundary, abundant vacuolated cytoplasm, and an eccentric nucleus. Papanicolaou stain. × 1,600

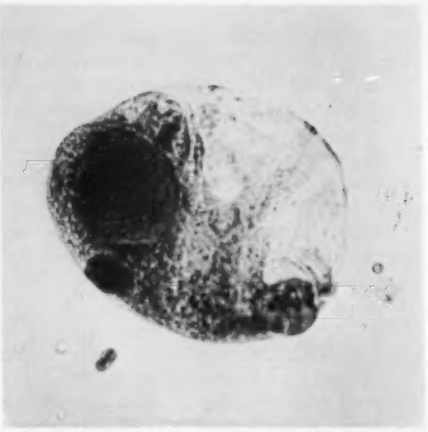

Fig. 3. Ventricular cerebrospinal fluid. Metastatic bronchiolar cell carcinoma. Quadrinucleated cell similar to that in Figure 2. The neighboring end-on red blood cell gives an idea of the large size of this carcinoma cell. Wet film, serum-toluidine blue stain. × 560 (approximate)

opinion was expressed that they were considered to be derived from a metastatic epithelial neoplasm rather than a glioma. At the time that this fluid was examined, we were unaware of the patient's history of melanoblastoma or that roentgenograms showed a mediastinal mass.

At necropsy, the brain contained numerous deep brown nodules of metastatic malignant melanoblastoma; they involved the cranial leptomeninges and bulged into the lateral ventricles. Microscopic study of the nodule on the dorsum of the left foot revealed amelanotic malignant melanoblastoma in the dermis.

Case 2. *Metastatic bronchiolar cell carcinoma.* A woman, age 29 years, was admitted to hospital on November 25, 1959, with a six-month history of headaches, nausea, and vomiting. She had been fully investigated at other hospitals during the previous six months, but no definite diagnosis had been made.

On examination, the principal neurologic findings were disorientation and severe limitation of vision. The clinical impression was that she had a frontal lobe tumor involving both cerebral hemispheres, but the possibility of diffuse cerebral disease was also entertained. Carotid arteriograms, pneumoencephalograms, and a ventriculogram were normal. Chest roentgenograms showed bilateral diffuse miliary mottling suggestive of pyogenic bronchopneumonia.

The cerebrospinal fluid from the right lateral ventricle contained many abnormal cells (Fig. 2). They were large, ranging from 15 to 50 μ in diameter, and possessed sharp outlines. The large eccentric nuclei were irregular in outline and hyperchromatic; the chromatin pattern was uneven, and prominent nucleoli were usually seen. The cytoplasm possessed single large, or many smaller, clear vacuoles. Metastatic adenocarcinoma was diagnosed.

This finding refocused attention on the abnormal chest film; it was now realized that the abnormality represented diffuse bronchiolar cell carcinoma. She died on December 12, 1959, and necropsy revealed diffuse pulmonary bronchiolar cell carcinoma, with metastases to the leptomeninges, brain, spinal cord, and many visceral organs.

Case 3. *Metastatic bronchiolar cell carcinoma.* A man, age 44 years, was admitted to hospital on August 8, 1958, with a ten-month history of lethargy, headaches, and disorientation. He had been investigated at another hospital and had undergone ventriculography and a posterior fossa exploration, but no definite diagnosis had been made. He was disorientated and aphasic and had left spastic hemiparesis.

A right carotid arteriogram was normal, but a ventriculogram on August 12 showed evidence of a right thalamic tumor. Craniotomy was carried out, and a tumor of the right thalamic region was partially excised.

The cerebrospinal fluid removed from the right

lateral ventricle contained cells (Fig. 3) similar to those found in Case 2; they were interpreted as adenocarcinoma. On microscopy, the tissue was considered to represent a papillary ependymoma, provided that there was no extracranial evidence of malignant disease. The patient died on August 15, 1958. At necropsy, both lungs contained numerous miliary nodules of bronchiolar cell carcinoma; there were several nodular metastases in the brain.

Cells of primary brain tumors were found in two specimens of ventricular fluid.

Case 4. *Astrocytoma, grade III.* On the basis of clinical findings and carotid arteriography, a space-occupying lesion in the right parietotemporal region was diagnosed in a woman age 59 years. At operation, a large right parietal astrocytoma, grade III (Kernohan) was excised according to its macroscopic limits; the patient died three days later.

Ventriculography, though unsuccessful, enabled 35 cc. of cerebrospinal fluid to be aspirated from the right lateral ventricle; it contained neoplastic cells (Fig. 4). These cells were 10 to 20 μ in diameter and were dominated by large, rather irregular, hyperchromatic nuclei which were often paired. The chromatin patterns were coarse, and nucleoli were often seen. The gray cytoplasm was always scanty, giving the cells indefinite boundaries. These cells were interpreted as being derived from a glioma, rather than from an epithelial neoplasm.

Case 5. *Pinealocytoma.* In January 1959, a pineaoma was diagnosed on clinical, radiologic, and operative evidence in a man age 24 years. He was treated by a right Torkildsen ventriculosubarachnoid shunt followed by irradiation.

On May 18, 1959, a ventricular tap obtained syrupy xanthochromic fluid which contained tumor cells (Fig. 5). They were about 11 μ in diameter and were dominated by hyperchromatic nuclei with coarse chromatin. The cytoplasm was scanty and took a pale gray stain, and its boundaries were rather poorly defined. Clusters of necrotic cells were seen in the smears, and it was felt that the patient had sloughed part of his tumor into the lateral ventricles.

He died five weeks later, and necropsy showed dissemination of the neoplasm into the third and fourth ventricles, the surrounding brain, and the leptomeninges. Histologic examination showed the tumor to be a pinealocytoma.

Two specimens of cerebrospinal fluid from the cisterna magna were examined, and 1 contained cells from an ependymoma.

Case 6. *Ependymoma.* On clinical and radiologic evidence, a fourth ventricle tumor was diagnosed in a girl age 8 years. A suboccipital craniotomy was carried out with subtotal removal of a tumor involving the floor of the fourth ventricle; histologically, this was an ependymoma.

Fig. 4. Ventricular cerebrospinal fluid. Cell of an astrocytoma, grade III. Notice the "woolly" cell boundary, scanty cytoplasm, and the pair of overlapping nuclei. Papanicolaou stain. × 1,250

At the time of the craniotomy, cerebrospinal fluid was aspirated from the cisterna magna and submitted for cytologic examination. It contained neoplastic cells (Fig. 6), which were characterized by the length of the cytoplasm and nuclei, the former terminating in fine unipolar processes. There was an occasional rosette. The nuclei were

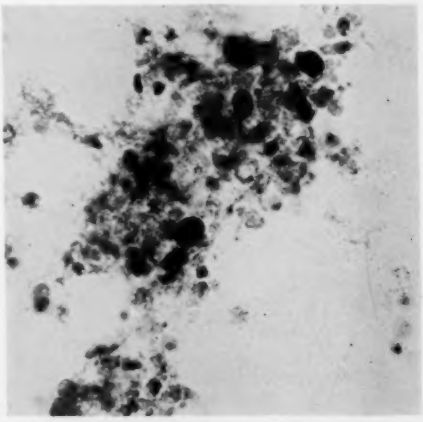

Fig. 5. Ventricular cerebrospinal fluid. A group of necrotic and viable cells of a pinealocytoma. Papanicolaou stain. × 510

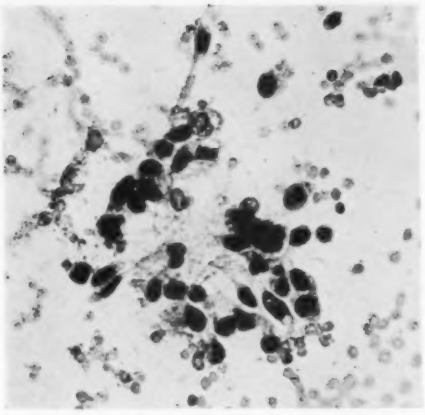

Fig. 6. Cerebrospinal fluid from cisterna magna. A group of cells of an ependymoma. These cells show a tendency to form a rosette and have long unipolar cytoplasmic processes. Papanicolaou stain. × 440

hyperchromatic with coarse chromatin. The cytologic diagnosis was a glioma, either ependymoma or medulloblastoma, the former being considered more likely.

A specimen of fluid from a pituitary cyst contained cells of a chromophobe adenoma.

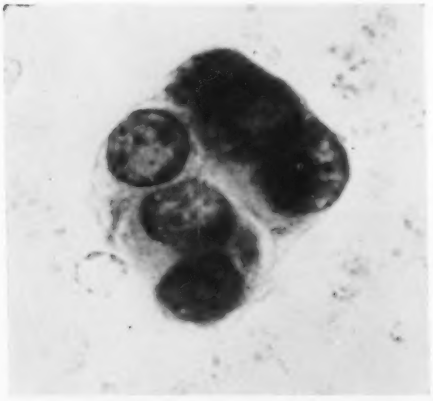

Fig. 7. Pituitary cyst aspirate. Groups of cohesive cells such as these suggested the epithelial nature of this neoplasm. Though not apparent from this photograph, the individual cells have a moderate amount of cytoplasm and sharp cell boundaries. Papanicolaou stain. × 1,530

Case 7. *Chromophobe adenoma.* A boy, age 17 years, with a six-year history of headaches was believed to have, on radiologic evidence, a parasellar mass.

Left frontal craniotomy was carried out, and what was considered to be a large aneurysm of the left internal carotid artery was identified. The left internal and external carotid arteries were ligated in the neck, and the former intracranially, in order to trap the "aneurysm." The "aneurysm" was needled, and what appeared to be pure blood was withdrawn and submitted for cytologic examination.

This specimen contained cells about 15 μ in diameter which were discrete or in cohesive epithelial-like clusters (Fig. 7). The nuclei were large and hyperchromatic and usually were situated eccentrically in the cells. Though dark, the chromatin did not possess the unevenness usually associated with cytologic malignancy. The cytoplasm was clear, and the cell boundaries were sharp. The cells were considered to be atypical epithelial cells.

The postoperative course was smooth, but there was no relief of headaches and he became blind in the left eye. In view of this and the unexpected cytologic findings, the diagnosis was revised to that of a cystic pituitary neoplasm. This belief was confirmed at reoperation when a pituitary chromophobe adenoma was partially removed.

Fluid of 6 cerebral cysts yielded tumor cells in 2 cases, 1 an astrocytoma and 1 an oligodendroglioma.

Case 8. *Astrocytoma, grade II.* On clinical and radiologic evidence, a right frontal tumor was diagnosed in a woman age 44 years. At operation, a right frontal gliomatous cyst was encountered which was subtotally removed; histologically, it was an astrocytoma, grade II.

At operation, 30 cc. of brownish fluid was aspirated from the cyst. This fluid contained neoplastic cells (Fig. 8); they were small, about 10 to 15 μ in diameter, and were practically all nucleus. Scarcely any cytoplasm was seen. The nuclei were often paired and atypical in that they were hyperchromatic and had a coarse chromatin pattern, prominent nucleoli, and slightly irregular outlines. Without any knowledge of the operative findings, they were considered to be malignant and derived from a glioma rather than an epithelial neoplasm.

Case 9. *Oligodendroglioma.* A man, age 55 years, had a left parietal craniotomy for recurrent oligodendroglioma. Cystic neoplasm was encountered in the left parietal area; 35 cc. of dark brown fluid was aspirated from the neoplasm.

This fluid contained many neoplastic cells, their diameters being about 10 to 15 μ (Fig. 9). These cells had scarcely any visible cytoplasm but were dominated by approximately round, hyperchromatic nuclei of such density that there was no perceivable unevenness in the chromatin. These cells were interpreted as being gliomatous.

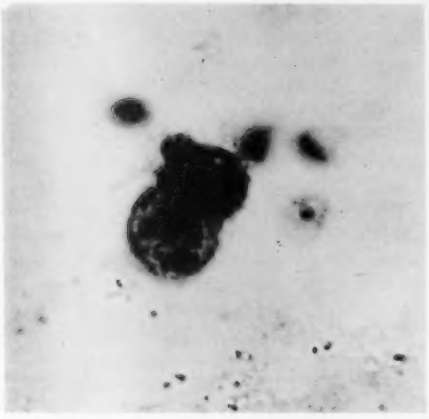

Fig. 8. Cerebral cyst aspirate. Cell of an astrocytoma, grade II, similar to the cell of Figure 4. This cell has an indistinct cell boundary, scanty cytoplasm, and a pair of nuclei which overlap. Papanicolaou stain. × 1,500

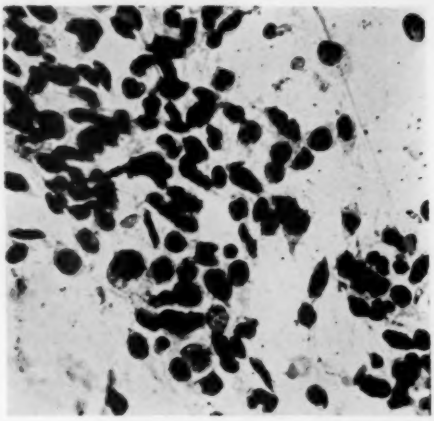

Fig. 9. Cerebral cyst aspirate. Cells of a recurrent oligodendroglioma. These cells are similar to the cells of the astrocytomas except that distinct pairs of overlapping nuclei are not seen and the nuclei are more hyperchromatic. Papanicolaou stain. × 690

A case of porencephalic cyst is included. It simulated neoplasm in its clinical manifestations, but the cytologic and histologic findings were characteristic of the benign cyst.

Case 10. *Porencephalic cyst.* A space-occupying lesion in the left frontoparietal region was diagnosed in a 20-year-old man. At operation, a large left frontoparietal cyst was encountered just beneath the leptomeninges, indenting the underlying cerebrum. There was no communication with the lateral ventricles. The cyst contained about 80 cc. of cloudy white fluid with many ciliated columnar cells (Fig. 10). These unusual cells were considered to represent immature ependyma, derived from either the ventricles or a cyst of ependymal origin. Histologic examination of the wall of the excised cyst showed it to be lined by ciliated columnar epithelium; it was considered to be a congenital porencephalic cyst, the etiologic factor in this patient's convulsive disorder.

DISCUSSION

Tumor cells were recovered from 9 intracranial fluids, from 1 benign and 8 malignant neoplasms. ("Benign" is used in a cytologic and not a prognostic sense.) The 12 benign neoplasms yielded tumor cells in only 1 case, that of pituitary adenoma. This was the only benign neoplasm of epithelial origin. There were 8 fluids derived from 34 cases of malignant intracranial neoplasms which contained tumor cells, a higher proportion than those recovered from benign neoplasms. Tumor cells were recovered from 3 of the 8 cases of metastatic neoplasm, whereas 5 of the 26 gliomas yielded recoverable cells (Table 3). There were no false-positive reports.

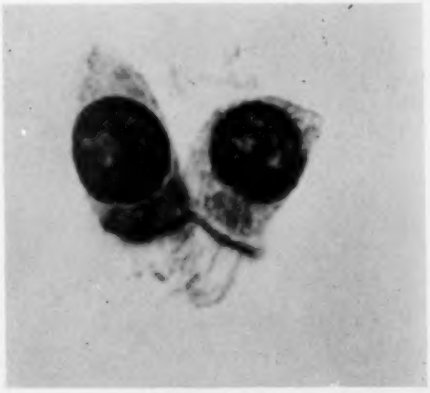

Fig. 10. Porencephalic cyst aspirate. Ciliated columnar lining cells. Papanicolaou stain. × 1,600

The metastatic tumors have a higher incidence of cell recovery than the primary malignant tumors of the brain. Could this higher incidence, especially in ventricular fluids, be due to the increased frequency of their encroachment on the walls of the lateral ventricles? Table 4 shows the frequency with which the gliomas and the metastases were known, on radiologic, operative, or necropsy findings, to encroach on the wall of the lateral ventricle from which fluid had been obtained and examined cytologically. Encroachment occurred in 5 cases of metastatic neoplasm and 8 cases of glioma; tumor cells were recovered in 3 and 2 cases, respectively. The evidence points to a tendency, well demonstrated in other areas of the body, of the malignant epithelial neoplasms to exfoliate their cells, as does the normal epithelium which gives rise to them. This tendency is presumed to be due to an inherent property of these neoplasms, a property which is possessed to a greater degree than in the gliomas.

Generally, it is not difficult to decide whether cells seen in an intracranial fluid are neoplastic; the cells with which they might be confused are few in type and do not show much morphologic variation. In the wet film, histiocytes are the most confusing. Sometimes they are quite large and take the blue stain heavily throughout both nucleus and cytoplasm. By careful scrutiny under high power, one should be able to discern the faint smooth outlines of one or more nuclei, and it will be seen that these cells have a low nuclear-cytoplasmic ratio. This in itself is good evidence that the cells are not malignant. It is realized that some adenocarcinoma cells may have a low nuclear-cytoplasmic ratio, but their nuclei are larger and more irregular in outline than those of histiocytes and the cytoplasm will usually present one or more vacuoles. Occasionally, histiocytes will be seen in clusters, especially in the wet films. This grouping is considered to be artifactual, due to the cells being thrown together during centrifugation, and should be easily distinguished from clumps of neoplastic cells by the rather ragged appearance of the edge of the group and by scrutiny of the individual cells at the periphery.

We have not been able to recognize discrete choroid plexus or ependymal cells with certainty; perhaps they round up when exfoliated and resemble lymphocytes or monocytes. On one occasion, a large papillary cluster of choroid plexus cells was seen which bore a superficial resemblance to adenocarcinoma; when the cells were examined under high power, their benign nature was obvious.

Normal glial cells are occasionally seen, especially in ventricular fluid; they have always appeared as fragments of brain, and the individual cells are recognized more or less by their nuclei as in routine tissue sections. Presumably, this fragmentation of brain substance is due to the transit of the ventricular needle. "Endothelial" cells are occasionally referred to in the literature, but I am not certain how they are identified. In samples of spinal fluid, we have occasionally seen bare, bland, oval nuclei. It is possible that these are "endothelial," but they may be another type of cell which has lost its cytoplasm during the technical procedures. Necrotic cells were seen only once, in the case of pinealocytoma.

Recently, McMenemey and Cumings[7] and Marks and Marrack,[8] using a Romanowsky stain, expressed the opinion that it is difficult to distinguish between the different types of tumor cells found in cerebrospinal fluid. This has not been our experience. In those cases in which we had no foreknowledge of the nature of the neoplasm, it was possible to decide correctly which neoplasms were of epithelial and which were of gliomatous origin.

TABLE 3

GLIOMAS AND METASTASES: CELL RECOVERY

	Number of cases	*Tumor cells recovered*
Gliomas	26	5
Metastases	8	3
Totals	34	8

TABLE 4

NEOPLASMS INVOLVING LATERAL VENTRICLES

	Number of cases	*Tumor cells recovered*
Gliomas	8	2
Metastases	5	3
Totals	13	5

The cells of Case 1 (malignant melanoblastoma) were reported as those of a malignant neoplasm of epithelial origin. Cases 2 and 3 (bronchiolar cell carcinoma) were reported as adenocarcinoma. In none of these cases had we any inkling of there being a neoplasm outside the cerebrospinal axis. The cells found in the aspirate of the "aneurysm" in Case 7 (chromophobe adenoma) were identified as atypical epithelial cells and were reported as such. The cells of Case 6 (ependymoma) and Case 9 (astrocytoma, grade III) were reported as glioma.

It became obvious that the main differences between the cells of the gliomas and the cells of the epithelial neoplasms reside in their size, outline, cytoplasm, and, to a lesser extent, grouping. The cells of the gliomas are generally smaller than those of epithelial neoplasms. They have indistinct, "woolly" boundaries, and their cytoplasm is scanty and usually stains to a moderate degree. In contrast, the cells of the epithelial neoplasms are large and possess distinct boundaries and relatively more cytoplasm, which, in the case of the adenocarcinomas, is pale staining and vacuolated. The cells of the epithelial neoplasms show a tendency to occur in cohesive clusters, whereas the cells of the gliomas are usually discrete. Differentiation on the basis of nuclear morphology seems unreliable, although we have noticed, as did McMenemey[15] in his touch preparations, the tendency of nuclei of the astrocytoma series to occur in overlapping pairs (Figs. 4 and 8). It is not intended to dwell upon the criteria which enable one to conclude that a cell is malignant; they are precisely the same as those applied to cells derived from other situations and systems of the body and can be found in textbooks.

Exfoliated cells of a squamous cell carcinoma were not encountered in this study; the 8 metastatic neoplasms were all adenocarcinomas. This is surprising in view of the fact that one can expect metastatic squamous cell carcinomas and adenocarcinomas in equal numbers in the central nervous system.[16] Even if there were cases of squamous cell carcinoma metastatic to the central nervous system, it is unlikely that exfoliated cells would be recovered. The basis for this supposition lies in the fact that the literature is devoid of reports of cells of squamous cell carcinoma being recovered from cerebrospinal fluid except for the anaplastic carcinoma, presumably of stratified squamous epithelial origin, arising from an intracranial "cholesteatoma" described by Ernst.[17] McMenemey and Cumings[7] described cells of a metastatic pulmonary "squamoid" carcinoma in cerebrospinal fluid, but the primary neoplasm had some features of adenocarcinoma.[18] Presumably, this failure of squamous carcinoma cells to exfoliate into cerebrospinal fluid is due to inherent properties of the neoplasm and finds a parallel in the failure, except on rare occasions, of cells of this type of carcinoma to exfoliate into serous fluid.

When the 10 cases presented here are considered, it is seen that in several the cytologic findings in the intracranial fluids had some actual or potential usefulness. In Case 1, a diagnostic problem was more or less terminated; complete finality might have been accomplished had we but known the antecedents of the case. Case 2 was brought to a definite and correct diagnostic termination; this might have been reached several months sooner had the cerebrospinal fluid of the first ventricular tap been appropriately examined. This latter statement would also apply to Case 3. The finding of the adenoma cells in the pituitary cyst of Case 7 played a large part in the decision to reoperate. The management of the cases of glioma appeared not to profit from any positive cytologic findings.

It seems that such cytologic examinations can be of most practical value in cases of obscure diagnostic problems, when intracranial neoplasm is suspected but there is no definite radiologic evidence of a localized lesion, as in Cases 1 and 2. This situation will obtain particularly with metastatic intracranial neoplasms, either when no primary is located or when a possible primary is known and it is desired to find out if there are metastases to the brain. With gliomas, the practical value of this type of examination is not as great; they are less likely to exfoliate their cells. They are usually adequately detected by radiologic methods, and, once this stage is reached, operation, with frozen sections of the neoplasm, provides the final diagnosis. An exfoliative cytologic examination of an intracranial fluid may have some usefulness in investi-

gation of cases of suspected recurrence of gliomas, when the question is whether neoplasm has recurred or whether the clinical condition is due to postoperative morbidity.

SUMMARY

A total of 76 intracranial fluids were examined by conventional methods of exfoliative cytology; 46 of the fluids were from patients with intracranial neoplasms. Tumor cells were recovered from 9.

Cells of metastatic intracranial neoplasms of epithelial origin are more likely to be recovered than those of gliomas. Morphologic differences between the exfoliated cells of metastatic epithelial neoplasms and gliomas are brought out.

The value of finding tumor cells in intracranial fluids is greatest in obscure diagnostic problems when localized intracranial tumors are not detectable; this situation is particularly liable to occur with metastatic brain tumors. Generally, there is little value attached to the recovery of cells from primary brain tumors.

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Multiple endocrine adenomas (Lloyd's syndrome) and psychomotor epilepsy

W. Kramer, M.D., and B. Makkink, M.D.

THE COMBINED PRESENCE of changes in the central nervous system and of multiple adenomas of the endocrine glands has not been reported before. For this reason, a case in which such a combination was present and also in which a relation between the two disease processes is likely is presented herewith.

CASE REPORT

The patient was a 37-year-old single woman who had been fit until 1945, when she had psychiatric treatment for endogenous depression. She had been otherwise healthy until the beginning of 1957, when occasional periods of confusion began, sometimes accompanied by epileptic seizures. She was seen for the first time in May 1958, when she presented a somewhat infantile and neurotic appearance. No neurologic abnormalities were found, but the electroencephalogram showed sharp waves in the left temporal region. However, roentgenograms of the skull were normal. A diagnosis of psychomotor epilepsy was made at this stage, and she was put on primidone and a phenacemide derivative (Trinuride). Notwithstanding this treatment, periods in which she was confused and reacted automatically continued and became more severe. There was no aura. The seizure began with staring; following this she would slip from her chair, wring her hands, and grimace. Often, her cheeks became red at this time. There was no incontinence or tongue biting, but amnesia and headache lasting for hours might follow the attack. Besides these attacks, she occasionally had a generalized epileptic convulsion.

In the middle of 1958, she was admitted to the neurologic ward, where again no neurologic changes could be found. The electroencephalogram showed a focus of dysrhythmia in the left temporal region, in which paroxysms of delta and theta waves 100 to 150 mv in amplitude were present. The pneumoencephalogram and a left angiogram showed no abnormalities, with the exception of slight atrophy of the dorsum sellae.

During the one month of clinical observation, no attacks were seen, although medication was discontinued. However, in October, about one month after the patient's discharge from the hospital, her mother reported that some days previously the patient had had a generalized epileptic seizure and subsequently an attack of confusion and abnormal behavior. On examination the same day at home, she was found to be in a dreamy state, unable to recognize one of us though she could answer simple questions. She was readmitted immediately.

In the hospital, she remained semicomatose and, at regular intervals, attacks of conjugate deviation of the head and eyes to the right with tonic extension of the right arm were observed. Meanwhile, right flaccid hemiplegia with general aflexia and bilateral plantar responses in extension were found.

The electroencephalogram (Dr. W. Storm van Leeuwen) showed paroxysms of slow high-amplitude waves, lasting about half a minute, mostly registered in a temporofrontal region, especially on the left side. They were only occasionally synchronous with a clinical attack. The ground rhythm was irregular (Fig. 1).

On account of the clinical manifestations and the paroxysmal electroencephalographic abnormalities, the patient's condition was diag-

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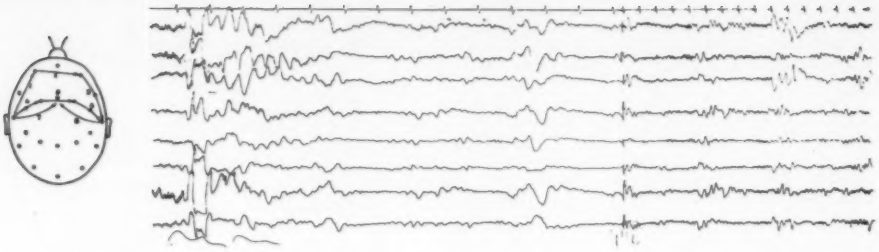

Fig. 1. Electroencephalogram during status psychoparalyticus. Periodic and paroxysmal discharge of slow waves

nosed as psychomotor epilepsy. Since all psychic functions apparently were abolished, it was called "status psychoparalyticus." Therapy consisted of barbiturates and antibiotics.

Moreover, while she was semicomatose, a rash was noticed time and again, spreading all over the body, lasting for about ten minutes. The pupils alternately were very wide and very narrow; the blood pressure fluctuated from 170/100 to 70/50 and the pulse rate from 168 to 70 per minute. The clinical picture could best be characterized as that of so-called "diencephalic epilepsy."

Twenty-four hours after admission, the attacks and the vasovegetative manifestations stopped, but the patient remained semiconscious and reacted only to pinpricks. She had flaccid paresis of all 4 limbs, with abolished reflexes but absence of pyramidal signs. The electroencephalogram was almost flat but was interrupted by paroxysms of delta waves, 1 to 3 per second, 200 to 300 μv in amplitude, lasting from one-fourth to one-half minute, predominantly in the left temporal region.

Ten days after onset of the semicomatose state, the patient, when requested to do so, opened her eyes; deep reflexes now were elicitable, but pathologic reflexes were evoked from both hands and feet. Improvement, however, did not go further, and she remained paralyzed and semicomatose. Because a diencephalic tumor was suspected, she was again thoroughly examined. As the sella turcica was slightly enlarged and its dorsum somewhat atrophic, ventriculography and right angiography were performed (W. Luyendijk) but revealed no abnormalities, the third ventricle and the suprachiasmatic cisterna specifically being normal. The cerebrospinal fluid showed no abnormality on 6 occasions. All other laboratory findings also were normal, with the exception of the fasting blood sugar, which

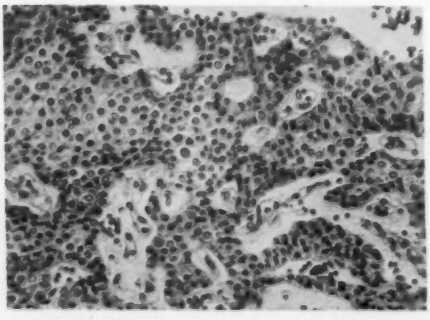

Fig. 2. Adenoma of parathyroid gland. Hematoxylin and eosin stain. × 800

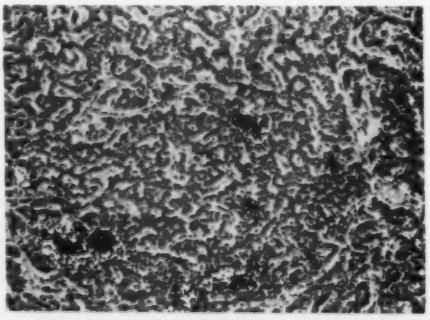

Fig. 3. Adenoma of islet cells of pancreas. Hematoxylin and eosin stain. × 400

was first 52 and later 63 mg. per 100 cc. Alkaline phosphatase content of the blood was 13 K.A. units. Calcium and phosphorus were not estimated.

As already mentioned, the patient never regained consciousness and did not communicate with even her mother. She had no facial expression and only grimaced on strong stimuli, whether pain, noise, or light. She had to be fed artificially, while her respiratory tract was kept clean by suction through a tracheotomy cannula. Both arms and legs were fixed in a slight flexion contracture by extremely rigid and wasted muscles. Magnus–de Kleyn reflexes were occasionally elicited in the right arm. Tendon reflexes were brisk, and pyramidal signs were present in all extremities. In this condition, often designated as "decorticate rigidity" in man, she was nursed till her death, without a certain diagnosis. She died half a year after the development of her psychoparalytic state and two years after the onset of symptoms, death ultimately being due to emaciation and bronchopneumonia.

Postmortem examination. On top of the left lobe of the thyroid gland was situated a small tumor, which on histologic examination proved to be an adenoma of the parathyroid gland (Fig. 2). It consisted mainly of solid masses of eosinophilic cells, but, at the periphery of the tumor, cells were vacuolized and, at another area, cystic structures containing blood were found.

In the pancreas, 2 small nodules could be seen macroscopically, but a large number of typical islet-cell adenomas composed of solid monomorphous cells arranged in cords were seen on microscopic examination (Fig. 3). A few adenomas contained hyalinized connective tissue fibers. Methanine-silver staining according to Hamperl demonstrated many alpha cells in the microscopically visible tumors. The 2 larger ones contained only beta cells.

In the anterior lobe of the hypophysis, another tumor the size of a pea was found which on microscopy was more or less characteristic of a chromophobe pituitary adenoma (Fig. 4). The sella turcica was not enlarged although its dorsum was very thin. Within the kidneys, small areas of calcification, somewhat fibrotic in structure, were found.

In the lungs, bronchopneumonic changes

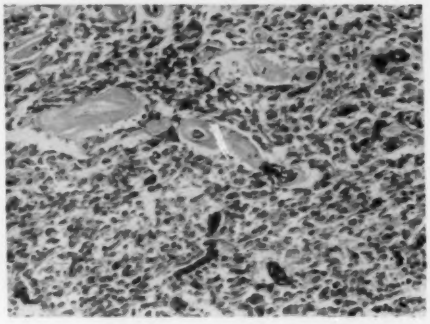

Fig. 4. Adenoma of pituitary gland. Hematoxylin and eosin stain. × 800

were seen. In the adrenals, the glomerular zone was small, whereas the fascicular zone was broad, its cells being hyperplastic and degenerated. The bone marrow showed a normal myelo- and erythropoiesis; slight osteoclastic resorption of bone and some replacement by connective tissue were seen.

The brain weighed 1,200 gm. and was slightly atrophic, with enlarged ventricles. From different parts of the brain, a number of slides were taken and stained with hematoxylin and eosin and cresyl violet and according to the technics of van Gieson and of Klüver and Barrera. Serial sections were made of the diencephalon, every tenth section being mounted and stained.

In all preparations, both in the gray and the white matter, the same changes were found, though differing in degree. In the cortex cerebri, many neurons were lost and others showed signs of degeneration (Fig. 5). Satellitosis and phagocytosis were frequently seen and contributed to an excess of glia cells. A normal lamination was practically absent, and the vestiges of edema were present, but there were no signs of inflammation in the brain. The overlying leptomeninx was slightly thickened, but, similarly, signs of infiltration were absent.

Loss of neurons and glial hyperplasia were especially marked in both hippocampi, Sommer's sector being entirely devoid of neurons (Fig. 6). The basal ganglia and thalamus showed the same alterations as the cortex but to a less severe degree. The gray matter of

the brain stem and cerebellum, however, were severely affected; loss of Purkinje cells was conspicuous, as was proliferation of Bergmann's glia cells.

The Klüver and Barrera stained preparations of the cerebral white matter showed a diffuse demyelination with fragmentation of the myelin sheaths. Moreover, multiple areas of edema with an excess of glia cells were seen.

In the serial sections of the diencephalon, the same alterations were found, although to a lesser degree than in the cerebral cortex, the supraoptic and paraventricular nuclei being only slightly damaged.

In the upper segments of the cervical cord, a severe atrophy of anterior horn motor neurons was noticed, evidently the cause of the extreme muscular atrophy.

Summarizing, there was a single adenoma of the pituitary, one of a parathyroid gland, and multiple adenomas of the insular pancreatic tissue. In the central nervous system, neuronal atrophy with concomitant alterations of the nerve fibers was general and especially distinct in the hippocampus.

DISCUSSION

According to Underdahl, Woolner, and Black,[1] multiple adenomas of endocrine glands were first described by Erdheim[2] in 1903. In 1954, the total number of cases reported was 28, with an additional 10 in which documentation was inadequate.[3]

In 12 of the 28 cases, the pituitary and parathyroid glands and the pancreatic insulae were all involved, either on clinical or postmortem evidence. The first such case was described by Lloyd[4] in 1929, this syndrome therefore often being given his name. In 8 only the pituitary and parathyroid glands, in 6 the parathyroids and the pancreatic insulae, and in 2 the pituitary gland and the pancreatic islets were involved.

The present case apparently is the tenth (Moldawer, Nardi, and Raker,[3] 8; Cooke and

Fig. 5. Cerebral cortex in a case of Lloyd's syndrome. Loss of stratification, edema, degeneration of neurons and glia. Hematoxylin and eosin stain. × 100

Fig. 6. Sommer's sector of right hippocampus. Almost total loss of pyramidal cells and spongy degeneration. Klüver-Barrera stain. × 500

associates,[5] 1) reported in which a number of adenomas were found in all 3 glands at postmortem examination. Besides its rarity, it is also of importance in view of the finding of neurologic abnormalities or tumors in many of the members of our patient's family.

The etiology of these adenomas is obscure, since a causal relationship between the presence of one adenoma in an endocrine gland and the consequent development of adenomas in the other glands is not established. Apparently, the most conceivable hypothesis advanced as yet is that of a genetic defect, to which cases with familial incidence lend support. In 6 instances in the literature (4 of Underdahl and associates,[1] 1 of Wermer,[6] 1 of Moldawer and associates[3]), such an incidence was presented. Wermer described a family in which the father and 4 of 9 siblings were affected. Moldawer came to the conclusion that these multiple endocrine gland adenomas are a genetic manifestation, while Wermer inclined to a dominant hereditary transmission, except that a single autosomal gene probably was responsible for the whole complex of alterations. To this syndrome several authors added a tendency toward tumors of other organs.

The family of our patient is shown in Figure 7. As far as available information goes, consanguinity seems to be absent in this family. The father died of Cushing's disease. Furthermore, epilepsy, oligophrenia, carcinomas, cerebral tumor, and foot deformities were found among relatives of our patient. The evidence for the diagnosis given does not rest on postmortem findings or endocrinologic studies. However, it remains most unusual to find such an accumulation of abnormalities in one family, suggesting that some hereditary factor may be involved. This suggestion is further strengthened by the above mentioned findings from the literature. It will obviously be of paramount importance to study this family in much greater detail, specifically including careful endocrinologic investigations.

Patients suffering from these multiple endocrine gland adenomas present a variable clinical picture, the combination of acromegaly and parathyroid adenoma being most common (11 out of 28 cases). Others either showed symptoms of a hypophyseal tumor or hypoglycemia (whether or not combined with a kidney affection). An unexpected feature of the syndrome is the high incidence of disorders of the alimentary tract encountered with it.[5]

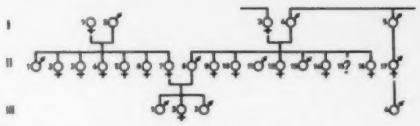

Fig. 7. Pedigree in a case of multiple endocrine adenomas. I 3, epilepsy; I 5, neurologic disease; II 1, carcinoma of esophagus; II 2, carcinoma of mamma; II 4, carcinoma of eye; II 5, diabetes; II 8, morbus Cushing; II 9, carcinoma of mamma; II 11, oligophrenia; II 16, epilepsy; II 17, cerebral tumor; II 8 and II 16, pes excavatus; III 2, patient with Lloyd's syndrome; III 4, dwarf.

The initial diagnosis of psychomotor epilepsy in the present case was especially due to the absence of clinical manifestations of endocrine disorder. Signs of a pituitary tumor were absent or too slight to be noticed, nor were those of parathyroid gland hyperactivity obvious. The cortical layer of the bones of the skull was roentgenologically not diminished in width, and symptoms of chronic renal insufficiency were not noticed, but the calcium content of the blood unfortunately was not examined.

At autopsy, small areas of calcification were found in the kidneys, possibly the result of a parathormone hypersecretion, which is also suggested by the microscopic finding of slight fibrosis of the bones.

The only biochemical abnormality observed in our patient during life was the blood sugar, which on first admission was found to be (fasting) 52 and 63 mg. per 100 cc. on 2 separate occasions (method of Hagedorn and Jensen). This low level undoubtedly was a sign of the presence of the insulinomas. A glucose tolerance curve at this stage also was unusual (fasting, 52; fifteen minutes, 81; thirty minutes, 130; sixty minutes, 184; ninety minutes, 125; one hundred and twenty minutes, 120; one hundred and fifty minutes, 118); this becomes comprehensible, however, in the light of the presence of both beta and alpha cells in the pancreatic adenomas, a pituitary ade-

noma, and hyperplastic and degenerative changes in the adrenals. During life, they would not readily be appreciated. It is regrettable that specific endocrinologic studies were not undertaken.

The question of the development of the cerebral changes and the clinical symptomatology in connection with the endocrine gland adenomas is very difficult to solve. Reports in the literature about the combination of these adenomas with cerebral changes are lacking and therefore the interpretation to be offered is speculative.

Possibly, initially, an endocrinopathy (adenomas) led to a paroxysmal central nervous system metabolic disturbance, presumably due to a lowering of the blood sugar level. This could explain the long episodes of confusion of the patient in the beginning, especially when she was fasting.

This hypoglycemia, being noxious to the brain, may be followed by a gradual reduction of the carbohydrates reserves and a decrease in oxygen uptake and of the high-energy phosphates available to the central nervous system.[7] It is reasonable that such disturbances, if frequent and prolonged, may cause irreparable neuronal changes.

Tokizane and Sawyer[8] and Meter, Owens, and Himwich,[9] studying the origin of hypoglycemic seizures in rabbits, demonstrated that hypoglycemic electrical seizures invariably originate in and may be confined to the amygdala or the hippocampus. This means that the seizure threshold of these structures is low for hypoglycemia, just as it is for electrical stimulation, cholinergic drugs, and many other stimuli. The morphologic changes following hypoglycemic attacks also are mainly situated in the hippocampus, as was experimentally shown by Stief and Tokay,[10] Lawrence, Meyer, and Nevin,[11] and Hicks.[12]

These examples suggest that, in our patient, the hippocampus was the part of the central nervous system primarily damaged. This might be the reason why the hypoglycemic periods assumed the character of psychomotor fits, as was also the case in a patient recently described by Boudin, Lauras, and Labet.[13]

It might be supposed that, subsequently, the psychomotor fits of our patient started spontaneously, without a primary metabolic disturbance eliciting them, and at a later stage developed into generalized seizures. Such a posthypoglycemic epilepsy has been described by Gibbs and Murray,[14] Cadilhac, Ribstein, and Jean,[15] and Yager and associates.[16] In the last instance,[16] it developed into status epilepticus, comparable to that seen in our patient.

Hippocampal seizures in their turn may produce responses in the hypothalamus, as has been experimentally demonstrated by Powell and associates.[17] So it may be fair to suggest that the vegetative phenomena during the status psychoparalyticus of our patient were the result of discharges in the hippocampus which spread to the hypothalamus, as evidenced by the electroencephalographic findings. It is probable that the vicious circle—disorder of metabolism, brain damage, spontaneous epileptic discharges, paroxysmal disregulation of the diencephalon, disorder of metabolism—led to so severe and irreversible changes in neurons all over the central nervous system during the status of psychomotor epilepsy ("catabolic encephalopathy") that a partial paralysis of psychomotor functions resulted. These irreversible changes were microscopically found at postmortem examination. It seems acceptable that they were partially due to the above mechanism and partially to periods of anoxemia during the status psychoparalyticus. They are sufficient substratum to explain the neurologic picture following this status.

SUMMARY

A 37-year-old woman died of bronchopneumonia and marasmus after a period of semiconsciousness of six months' duration. At postmortem examination, multiple adenomas of the pancreas, 1 of the parathyroid glands, and 1 of the pituitary gland were found. Her father had died at the age of 37 with signs of Cushing's disease. Moreover, in the family, oligophrenia, epilepsy, carcinomas, cerebral tumor, and degenerative signs occurred. Clinically, the diagnosis in our patient was not made, as the adenomas were neither manifested by local symptoms nor by stationary endocrine abnormalities. A paroxysmal disturbance of metabolism (hypoglycemia) caused irreversible changes in the brain, especially of the

hippocampus. These in their turn were accompanied by psychomotor fits, culminating in a status. The microscopic studies revealed how the biochemical events were engraved into the brain substance. From a clinical point of view, this case shows that even partial epileptic seizures (psychomotor fits) may be caused by an impaired regulation of the general metabolism.

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Beta-glucuronidase activities in tumors of the nervous system

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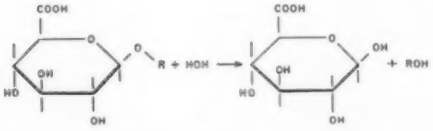
In attempts to search for possible biochemical characteristics of nervous system tumors, it has seemed appropriate to study the activities of those enzymes which have been found to undergo changes in activities in the neoplastic process as affecting other organ systems. Cytochrome oxidase[1] and dehydropeptidase I,[2] 2 such enzymes, have already been studied. The present report is concerned with an investigation of total beta-glucuronidase activities in a group of specimens representing most of the neoplastic types encountered in nervous tissue.

Beta-glucuronidase acts to catalyze the hydrolysis of the beta linkage between glucuronic acid and an aglycone as indicated in the following equation:



The aglycone may be any one of a great variety of compounds including phenol, menthol, borneol, monohydric and polyhydric alcohols, steroids, and many others.[3] The beta-glucuronosidic linkage is the only form occurring in nature. The enzyme itself is widely distributed in all animal tissues, being of particularly high activities in spleen, liver, uterine epithelium, intestinal mucosa, and endocrine tissues. It is markedly elevated in a wide variety of neoplasms in comparison to the respective tissue of origin.[4]

As in previous endeavors, the general approach has required use of a quantitative histochemical technic so as to provide the closest possible histologic correlations and to insure the elimination of the possible contaminating influences of large areas of necrosis, hemorrhage, or invaded brain tissue.

METHODS

Collection of material. All material was obtained directly at time of surgery using specially cleaned containers. Most of the tumor specimens were removed en bloc, a few by forceps. Blocks of grossly normal cerebral cortex and subcortical white matter were obtained from portions of brain excised in the course of approaching deeply seated neoplasms. None of the specimens here treated were obtained after shock or prolonged hypotension. A great majority were obtained while the subject was under general anesthesia, but in 2 instances material was obtained under local anesthesia. It would not be anticipated that any of these agents would influence the activity of the enzyme, and, indeed, a comparison of similar tumors and of corresponding areas of brain obtained under a variety of combinations of anesthetics or lack of general anesthesia indicates that no discernible effect of these agents can be found. Most of the specimens were received by the author at operation and transported in a container at 0° at once to the laboratory where the specimen was quickly dissected into blocks and quick frozen in dry ice for storage at -60° C. For each block saved for biochemical study, an adjacent block was placed in fixative for histologic examination. This afforded the first histologic control. In the case of specimens ob-

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tained from the service of Dr. Eben Alexander of the Bowman Gray School of Medicine, all samples were obtained en bloc and immediately frozen in a deep freeze machine. After one to four days, these samples were transported in a dry ice container to the author's laboratory where they were then placed directly into dry ice storage at –60° C. In regard to these latter specimens, the author is greatly indebted to Dr. Martin Netsky for his descriptions and interpretations of material removed at the same operations and for providing access to his histologic material for comparison with our own samples.

Histologic methods. Fixatives used included alcohol formalin, formalin, Zenker's solution, and formalin ammonium bromide. Staining methods employed included thionin stain for Nissl substance, hematoxylin and eosin, phosphotungstic acid hematoxylin, Weil's myelin stain, Holzer's stain for glial fibrils, Bodian's method for neurofibrils, Holmes' silver nitrate for neurofibrils, Cajal's gold sublimate, Laidlaw's and Perdrau's stains for reticulin, Oil Red O, Luxol fast blue, MacManus' periodic acid–Schiff reaction, and the Luxol fast blue-periodic acid-Schiff-hematoxylin of Margolis and Pickett. As a qualitative staining comparison with the quantitative technic, the histochemical method of Seligman and associates[5] for beta-glucuronidase was used on many of the specimens.

Quantitative histochemical technic. As in previous endeavors, the technic of Linderstrøm-Lang[6] and Holter was employed. The sample employed was transferred to a cryostat at –18° C., and, with a stainless steel tissue punch, a cylindric block of tissue was prepared having diameter of 2.2 mm. and length of 3 mm. or more. The block of tissue surrounding this cylinder was removed, thawed, and fixed in an appropriate fixative. This constituted the second histologic control. The cylindric block of tissue was sectioned serially at 40 μ. Each set of sections included an initial section placed upon an albuminized slide for subsequent fixation in alcohol formalin and staining with thionin. This, therefore, constituted the third and ultimate histologic control. The second section was placed in a microtube having internal diameter of 3 by 27 mm. for enzyme study. The third section was placed upon a clean dry slide for subsequent drying in a desiccator for a minimum of forty-eight hours, after which dry weight was determined using a cantilever type quartz fiber microbalance of 0.1 μg. sensitivity. The fourth section was placed in a microtube to be used as a blank. The usual practice was to obtain at least 8 such sets from each block. In many instances, complete serial section of the block was indicated and as many as 20 such sets were obtained. After completion of the experiment, the histologic control sections were examined in conjunction with the tissue which had surrounded the cylindric block. In this way, it was possible to determine if the experimental tissue was compatible in composition to portions of adjoining blocks, if necrosis or hemorrhage was present, or if the specimen consisted rather of adjoining brain tissue. In some instances, histologic quantitations were necessary. In the case of a choroid plexus papilloma, where it was necessary to estimate the contributions of connective tissue cores of the papillae and of a colloidal secretory material, the images of the circular sections were projected upon uniform paper and the outline of connective tissue areas (or secretory material) was sketched. When cut out and weighed, the weight of the given tissue area in respect to the whole was taken as an index of volume per cent of the given tissue. In some instances a relative quantitation of cell populations was necessary. In this case, cell counts were made using a calibrated ocular reticule micrometer with correction for shrinkage due to fixation, as previously described.[2] Since the counts in this study were relative rather than absolute, the correction of Abercrombie[7] for sectioned nuclei was not invoked. When the control section from a given set was found to be unsatisfactory for any reason, that set was discarded. In the course of investigation, it was found that the presence of a small amount of necrosis in a glioblastoma multiforme produced no effect upon enzyme activity of the section. Nevertheless, a standard was arbitrarily set permitting no more than 5 volumes per cent necrosis in a glioblastoma multiforme. Similarly, it was found that an astrocytoma in which some neurons had been incorporated showed no difference in total activity as compared with

a pure sample, again providing the quantity of contaminating tissue was small. A standard was set allowing no more than a 1 to 200 ratio of nerve cells to tumor cells in such specimens.

Biochemical technic. The method derived has been a microadaptation of the basic method of Fishman, Springer, and Brunetti,[8] using phenolphthalein mono-beta-glucuronide as substrate with spectrophotometric measurement of the liberated phenolphthalein in alkaline solution. As finally adopted, the method is quite similar to that previously published by Wattenberg and Glick.[9] After the insertion of tissue sections into microtubes within the cryostat, the tubes are removed to a room at 4° C. where dumbbell-shaped glass beads of about 1-mm. diameter are inserted to facilitate subsequent operations; 5 microliters of 30% glycerol (after Wattenberg and Glick[9]) is added to each experimental and blank tube, and they are left in the cold room for one hour. Thereafter, in groups of 2, each experimental tube receives 5 microliters of 0.01 molar phenolphthalein mono-beta-glucuronide (Sigma) and 40 microliters of 0.1 molar acetate buffer *p*H 4.5. The tubes are covered with rubber caps, and mixture is achieved by buzzing.[10] Each tube is then placed in a slot in a wooden block within an incubator at 37° C. for a period usually of four hours but in a few cases varying with the activity of the sample. Blank tubes contain only the acetate buffer without substrate and are incubated for a similar period. After incubation, tubes are returned to the cold room at 4° C. where 100 microliters of 0.4 molar glycine buffer at *p*H 10.47 is immediately added with mixing by buzzing.[10] The tubes are capped with parafilm and centrifuged for five minutes at 2,800 rpm. An amount of supernatant of about 100 microliters is then transferred to a Lowry-Bessey microcuvette of 1.5-mm. width and optical density is determined at 555 $m\mu$. The blank readings, which are exceedingly low, are subtracted from the experimental value. A standard curve was prepared using various dilutions of phenolphthalein solution prepared with identical proportions of the experimental reagents used. Activities are calculated in terms of micrograms of phenolphthalein liberated per hour per milligram of dry weight.

The present technic differs in several ways from the method of Fishman, Springer, and Brunetti.[8] Tissue slices have been used instead of an homogenate, comparison between the 2 preparatory methods showing that no decrease in activity occurs in the sections. A single thawing of the tissue section has been used rather than the alternate freeze-thawing 9 times as practiced by Fishman.[8] In the conditions here employed, no additional activity could be released by the added freeze-thawing. Precipitation of protein by chemical means has not been used. In the first place, it is quite unnecessary since centrifugation of tissue sections results in a supernatant having an extremely low blank reading (optical densities in range of 0.007 to 0.014). Secondly, the author has noted that chemical precipitation of protein results in a binding of the liberated phenolphthalein to the precipitate, in small quantities at the tissue concentration used but in highly significant quantities for larger concentration. Various "activators" have been tried during the extraction phase including water, saponin, chloroform, chloroform methanol, and glycerol. Of these, glycerol has been found to give the highest activities and has, therefore, been utilized.

The author doubts that the activating effect of glycerol is due to improved extraction. It is more likely explained by the finding of Fishman and Green[11] that many monohydric and polyhydric alcohols participate in a transferase reaction with beta-glucuronidase and accelerate the hydrolysis of substrate. In the present technic, only the hydrolytic function of the enzyme would be measured. In order to be sure that the addition of glycerol does not change the results in comparing different tissues of different activities, samples of normal brain and benign and malignant tumors of widely varying activities were compared using alternate sets extracted by glycerol and by water. It was found that with water extraction, activities range between 81 to 96% of those with glycerol extraction but that the relative proportion of enzyme activity between the various tissues was unchanged with the 2 methods.

A linear relationship has been obtained with phenolphthalein liberation in respect to incubation time (Fig. 1) and tissue concentration (Fig. 2) over the entire ranges employed. The

method is highly sensitive, easily permitting the use of tumor samples of as little as 10 μg. of dry weight. In very homogenous tissues, high reproducibility was found as in the case of a series of 14 determinations on a quite uniform neuroblastoma in which a coefficient or variation of only 2.4% was achieved. It is therefore considered that the present technic is a satisfactory quantitative histochemical method for the demonstration of beta-glucuronidase activity, having the virtues of simplicity, sensitivity, and good reproducibility.

Nomenclature. Although the author does not imply any complete endorsement of any one classification here presented, it has seemed advisable to use a nomenclature in keeping with present concepts and with sufficient detail to permit some descriptive range. Consequently, for the most part, the classification of Russell and Rubinstein[12] is followed with two exceptions. Under the group of glioblastoma multiforme, each specimen has been followed by a qualifying adjective or phase indicating the principal cytologic characteristic within the experimental specimen. In the meningioma group, the classification of Cushing and Eisenhardt[13] has been followed.

RESULTS

Normal tissues. Although a detailed analysis of the intralaminar distribution of beta-glucuronidase in human and rat cortex is the subject of another communication, some mean figures for histologically intact samples of brain from frontal lobe are included in Table 1 for comparative purposes. In brief, it is noted that all of the cortical layers show values close to the mean figure of 0.56 μg. per hour per milligram of dry weight except for layer one and the lowermost layers. As subcortical white matter is gradually approached, enzyme level rises until it reaches the figure of approximately twice that of cortex. The relatively higher values in samples of layer one were found not to be due to the molecular layer but to contaiminating amounts of pia-arachnoid. After a number of attempts, it was possible to catch the first intact section off the pial surface for enzyme analysis. This was composed principally of pia-arachnoid and is reported in Table 1 as 0.82, which must be considered a minimal figure for this tissue.

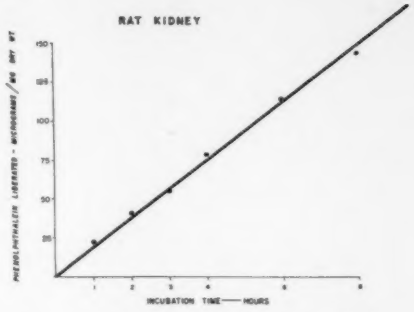

Fig. 1. Frozen tissue sections from Swiss albino rat kidney were cut at 20 μ and incubated at varying time intervals.

Tumors. Table 1 contains results acquired from the analysis of 39 frozen blocks obtained from 35 tumors. After the principal designation of most of the tumors, a qualifying adjective or phase is added for more detailed classification. The numerals in parentheses after each of the astrocytomas, glioblastomas multiforme, and ependymomas refer to the grading of the specimen after the criteria of Kernohan and Sayre.[14] The number of determinations refers only to those sets found to be acceptable. In general, it will be noted that the activities of beta-glucuronidase are

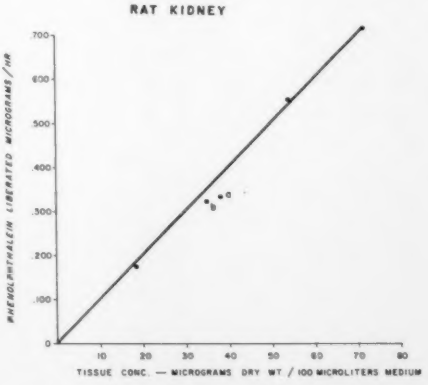

Fig. 2. Sections of Swiss albino rat kidney were incubated for two hours. Incubation tubes contained 1 to 4 sections at 20 μ. At point a, 2 sections at 20 μ were used and at point b, 1 section at 40 μ.

TABLE 1

BETA-GLUCURONIDASE ACTIVITIES IN NORMAL TISSUES, TUMORS, AND NECROSIS

Tissues	*Specimen number*	*No. of determinations*	*Beta-glucuronidase (μg. per hour per mg. of dry weight)*	*Standard deviation*	*Histologic description*
Normal					
Cerebral cortex	T-21		.56		
Subcortical white matter	T-21		.94		
Pia-arachnoid	T-51		.82		
Astrocytic					
Astrocytoma, fibrillary diffuse (1)	T-27	12	4.08	.51	Frontotemporal. Uniform appearance, moderate cellularity, small oval nuclei, stellate and elongated cells with glial fibrils
Astrocytoma, fibrillary, cerebellar (1)	T-32	9	1.10	.15	Cerebellar cyst with mural nodule. Uniform slender cells in whorls and interlacing bundles. Abundant glial fibrils.
Astrocytoma, protoplasmic (1)	T-29	10	1.71	.29	Temporal. Infiltration of cortex and white matter. Uniform oval nuclei. Cells varying from small with stellate processes to moderately abundant cytoplasm
Astrocytoma, protoplasmic (1)	T-66	6	4.68	.54	Thalamus. Loosely arranged delicate stellate protoplasmic astrocyte. Rare fibrils. Few foci of neoplastic oligodendrocytes
Astrocytoma, anaplastic (2)	T-25	12	2.99	.50	Parietal. Mostly uniform cells with delicate stellate processes. Focal pleomorphism and multinucleation. Rare mitoses
Astrocytoma, anaplastic (2)	T-33	8	3.29	.53	Frontal. Uniform gemistocytic astrocytes, moderate glial fibrils. Focal pleomorphism, endothelial hyperplasia
Astrocytoma-oligodendroglioma, recurrent, anaplastic (2+)	T-58	12	4.37	.52	Parietal cystic tumor. Moderately pleomorphic gemistocytic fibril-producing astrocytes, interdigitating with slightly anaplastic oligodendrocytes. Few mitoses
Astrocytoma, juvenile pilocytic, cerebellar (2)	T-64(a) T-64(b)	4 6	8.01 6.6	.33 .49	Shaggy cerebellar cyst in 11-year-old boy. T-64(a) and (b) composed of elongated strands and whorls of pilocytic astrocytes, pleomorphism and moderate cellular density. Rosenthal fibers (Fig. 3)
Oligodendrocytic					
Oligodendroglioma	T-31	12	3.26	.93	Frontal white. Densely packed uniform cells with small nuclei and clear cytoplasm in "halo" arrangement. Focal calcification. Reactive astrocytes
Glioblastoma multiforme					
Glioblastoma multiforme, protoplasmic (3)	T-55	5	7.50	1.80	Parietal. Densely cellular but rather uniform. Stellate astrocytic cells. Vascular hyperplasia, pseudopalisading, hemorrhage, mitoses
Glioblastoma multiforme, pilocytic (3)	T-28	5	10.08	1.24	Parietal. Spindle-shaped cells in whorls with occasional multinucleation. Pseudopalisading, frequent mitoses
Glioblastoma multiforme, spindle cell (3)	T-36	9	6.73	.96	Centrum ovale. Cellular. Spindle cells, fairly uniform, occasional multinucleation, occasional mitoses, vascular hyperplasia
Glioblastoma multiforme, cerebellar (3)	T-64(c)	14	14.3	1.04	Cerebellar cystic tumor. T-64(c) composed of dense cellular portions with pleomorphism of cells and nuclei, giant cells (Fig. 4)
Glioblastoma multiforme, gemistocytic (3)	T-24	4	25.7	1.75	Centrum ovale. Large gemistocytic cells, glial fibrils, 10% bizarre forms, some giant cells, mitoses, vascular hyperplasia
Glioblastoma multiforme, gemistocytic (3)	T-23(a)	9	14.55	1.11	Parietal centrum. Mixed glioblastoma-fibrosarcoma (Fig. 5). T-23(a) composed predominantly of pleomorphic gemistocytic astrocytes with fibrils
Glioblastoma multiforme, gemistocytic (3)	T-56	3	12.77	.65	Parietal centrum. Anaplastic gemistocytic astrocytes, few glial fibrils, occasional multinucleation and abnormal mitoses. Vascular hyperplasia
Glioblastoma multiforme, gemistocytic (4)	T-59	1	15.3		Frontal. Very anaplastic cells, mainly gemistocytic. Vascular hyperplasia, focal necrosis, giant cells
Glioblastoma multiforme, astroblastic (4)	T-37	5	16.25	1.0	Temporal. Poorly differentiated cells, some gemistocytic, some as

Glioblastoma multiforme, gemistocytic (4)	T-59	1	15.3		Frontal. Very anaplastic cells, mainly gemistocytic. Vascular hyperplasia, focal necrosis, giant cells
Glioblastoma multiforme, astroblastic (4)	T-37	5	16.25	1.0	Temporal. Poorly differentiated cells, some gemistocytic, some astroblastic. Rare anaplastic oligodendrocytes. Vascular hyperplasia. Abnormal mitoses
Glioblastoma multiforme, mixed glial (4)	T-43	8	21.4	.92	Parietal centrum. Densely packed very anaplastic cells, mainly pilocytic. Focal anaplastic oligodendrocytes. Hyperchromatism, giant cells, abundant mitoses
Glioblastoma multiforme, giant cell inclusion body (4)	T-51	2	32.7		Frontal centrum. Huge, bizarre giant forms with multinucleation. Eosinophilic intranuclear inclusions (Fig. 6). Basophilic cytoplasmic inclusions (Fig. 7)
Ependymal					
Ependymoma (1)	T-39	6	11.10	.79	Fourth ventricle, infant. Polygonal cells with uniform nuclei. Pseudorosettes and true rosettes
Ependymoma, malignant (3)	T-52	6	9.80	1.33	Frontal. Polygonal cells with eosinophilic cytoplasm and oval nuclei. Pseudorosettes. Endothelial hyperplasia. Frequent mitoses
Ependymoma, malignant (4)	T-40	7	12.71	.89	Parietotemporal. Ependymal type but quite anaplastic. Perivascular pseudorosettes. Mitoses, numerous giant cells
Choroid plexus papilloma	T-30	11	28.9	3.0	Cerebellopontine angle. Papillary formation with loose connective tissue cores covered by cuboidal-columnar epithelium, vacuolated. Mucoprotein between papillae (Fig. 8)
Other malignant tumors					
Medulloblastoma	T-22	7	9.09	1.19	Midline cerebellum. Densely cellular sheets of hyperchromatic nuclei with sparse cytoplasm. Mitoses. Subarachnoid and ventricular implants
Neuroblastoma, peripheral	T-60	14	12.8	.31	Right adrenal. Uniform, densely cellular tumor. Small cells, hyperchromatic nuclei. True rosettes
Fibrosarcoma	T-23(b)	8	17.7	2.36	Predominantly fibrosarcomatous portions of mixed glioblastoma-fibrosarcoma. Whorls of elongated, pleomorphic, multinucleated cells producing abundant collagen
Nerve					
Schwannoma, type A, root	T-63	7	14.2	.87	Dorsal root, T10. Interlacing whorls of elongated cells with fusiform nuclei, Antoni Type A
Schwannoma, type A, acoustic	T-65	9	8.21	1.55	Acoustic nerve. Elongated uniform cells in whorls, occasional palisading. Antoni Type A
Meninges					
Meningioma, meningothelial, type I, variant 4	T-35	7	7.25	.53	Olfactory groove. Polygonal cells in sheets and alveoli, minimal whorl formation. Collagen limited to septa
Meningioma, meningothelial, type II, variant 2	T-49	8	7.61	.60	Sphenoid wing. Polygonal cells arranged in sheets and whorls with a few psammoma bodies. Rare mitotic figures
Meningioma, meningothelial, type II, variant 1	T-62	11	7.23		Olfactory groove and multiple falcial. Polygonal cells in whorls with many small psammomas
Meningioma, angioblastic	T-45	5	3.36	.39	Anterior fossa. Uniform cells with well outlined boundaries, cytoplasm varying from eosinophilic to foamy or clear (Fig. 10). Occasional mitoses. Extensive reticulin network (Fig. 11). Highly vascular. Small blood channels lined by single layer of tumor cells
Secondary tumors					
Melanoma, metastatic	T-38	11	56.4	7.3	
Breast carcinoma, metastatic	T-44	10	24.3	3.97	
Chordoma, invasive	T-57	2	9.05		
Necrosis					
Total necrosis in glioblastoma multiforme	T-20	3	10.8	.9	
Total necrosis in glioblastoma multiforme	T-51	12	19.8	3.2	

higher in all of the tumors than in any of the 3 types of normal brain tissue. All malignant tumors tend to be high, whereas some considerable variation is noted among the well differentiated gliomas in respect to histologic type.

All of 4 well differentiated astrocytomas studied yielded values higher than those of normal brain but lower than those of overtly malignant tumors. The range has extended from approximately the level of subcortical white matter to a figure of about 5 times its activity. It should be pointed out that the value of 1.71 for protoplasmic astrocytoma T-29 is probably too low by virtue of an artifact of weight. This specimen consisted of tumor which had invaded subcortical white matter with enough persisting myelinated fibers to increase the dry weight above that expected in a pure tumor of this type. On the other hand, protoplasmic astrocytoma T-66 consists only of protoplasmic astrocytes in well differentiated uniform pattern free of myelinated nerve fibers or any other interfering tissue. It would be quite reasonable, therefore, to consider the value of 4.68 for this tumor as representative of a maximal figure for a sample of ultimate purity.

The first 2 (T-25 and T-33) of 4 astrocytomas with varying degrees of anaplasia were composed principally of well differentiated uniform astrocytes; however, the presence of small foci of pleomorphism required the designation anaplastic. The enzyme activities obtained for these 2 specimens fall entirely within the range of the well differentiated astrocytomas without histologic anaplasia. Sample T-58 was a mixed astrocytoma-oligodendroglioma which had originally appeared well differentiated but which upon operation after recurrence showed unequivocal anaplasia, more diffuse than the preceding 2 samples, but not sufficient to justify the term glioblastoma multiforme. The enzyme value of this sample also fell within the range of the well differentiated astrocytoma group. Samples T-64 A and B are derived from relatively well differentiated areas of an astrocytic tumor of cerebellum in an 11-year-old boy; despite its great rarity, it has been regarded as malignant (Fig. 3). These 2 samples were not from overtly malignant areas but rather were composed of thin, greatly elongated cells showing some tendency toward palisading but with the presence of some perivascular astrocytic processes. According to the concepts of Russell and Rubinstein,[12] this was designated a juvenile pilocytic cerebellar astrocytoma. The 2 blocks were similar histologically, and in each case enzyme activity was greater than that seen in other astrocytomas, being, in fact, at the lower limits of the glioblastoma multiforme group.

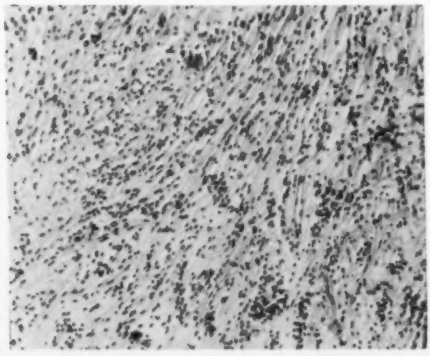

Fig. 3. T-64. Portion of a cerebellar tumor considered to be pilocytic astrocytoma, grade 2. Hematoxylin and eosin. × 150

The single well differentiated typical oligodendroglioma studied contained a few astrocytes which were probably reactive rather than neoplastic. The beta-glucuronidase activity of this tumor fell within the range of the well differentiated astrocytomas.

All instances of glioblastoma multiforme showed values of beta-glucuronidase activity markedly exceeding activities of normal brain and greater than any example of well differentiated astrocytoma. The range within the group is quite wide, extending from levels of 6.73 to 32.7. With attention to some subtypes of this class of tumors, one may roughly point to 3 general levels of enzyme activity. The first level would be 10 or below and would include some specimens which, while containing the classic characteristics of glioblastoma multiforme, were nevertheless composed predominantly of cells easily recognized as displaying astrocytic characteristics, in 1 case (T-55) protoplasmic forms, in another (T-28)

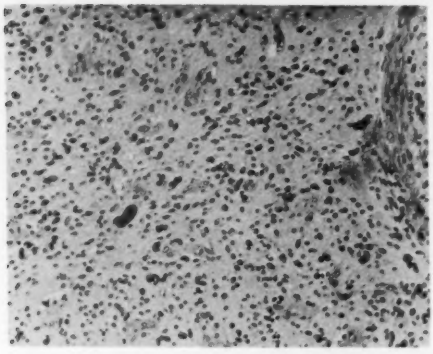

Fig. 4. Another part of specimen T-64 showing tumor giant cell, cellular pleomorphism, and vascular hyperplasia. This area was considered glioblastoma multiforme (astrocytoma, grade 3). Hematoxylin and eosin. × 150

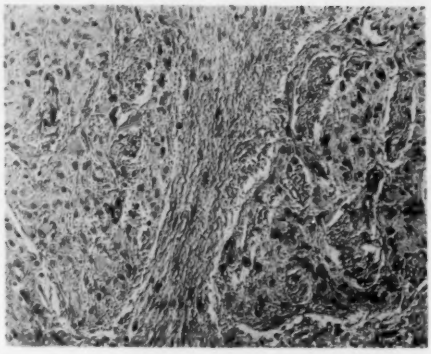

Fig. 5. T-23. Areas of gemistocytic fibril-producing glioblastoma interdigitate with zones of collagen-forming pleomorphic spindle cells. Phosphotungstic acid hematoxylin. × 150

pilocytic. A third specimen in this range was composed of spindle cells not producing fibrils but of rather uniform appearance. A second group within the range of 12 to 25 units includes all of the glioblastomas whose predominant cytologic characteristic was that of abundant cytoplasm of the gemistocytic type, together with 1 specimen containing quite anaplastic forms having the astroblastic histologic arrangement. Another specimen appearing to have mixed glial elements and the malignant-appearing portion of a juvenile cerebellar astrocytoma also fall within this range (Fig. 4). A third level might perhaps be considered that represented by the solitary giant cell inclusion body variety of glioblastoma multiforme,[15] the mean value of which we have placed at 32.7. This specimen constituted the only exception to our rule of excluding tumors having necrosis above the stated tolerance. The rarity of this type in our own experience and our use of a portion of the specimen for virologic studies left us with but a single sample; 20 series of sets studied on this sample were found to show extensive necrosis in all but 2. These 2, reported in Table 1, contained about 50% viable and typical tumor (Figs. 6 and 7). The totally necrotic sections showed a much lower enzyme activity. The reported figure may, therefore, be taken as a minimal figure of true activity. Since it was possible to determine the level of

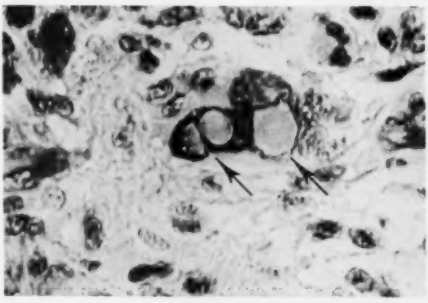

Fig. 6. T-51. Giant cell inclusion body type of glioblastoma multiforme. Arrows indicate eosinophilic intranuclear inclusions. Hematoxylin and eosin. × 800

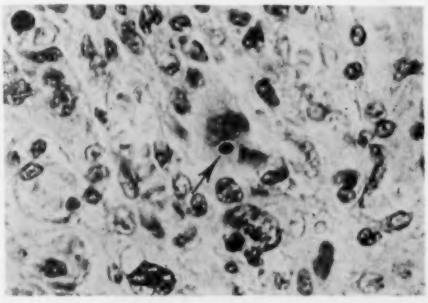

Fig. 7. T-51. Arrow indicates basophilic intracytoplasmic inclusion. Hematoxylin and eosin. × 800

activity in the totally necrotic portion, a correction could then be made for viable tumor tissue. Such an estimation would yield the figure of 48.5 units, a figure higher than that obtained for any other primary nervous system tumor of our series. One must recognize, of course, that this latter figure constitutes a rational estimate but by no means a proved value. Within the series of glioblastoma multiforme, then, one may distinguish tumors with low range of activity including those composed either of uniform or of rather well differentiated cells, an intermediate group containing poorly differentiated cells and all of the malignant gemistocytic tumors, and a very high range represented by the solitary, intensely anaplastic, giant cell inclusion body glioblastoma.

A series of ependymomas of varying stages of differentiation proved to be quite different from tumors either of astrocytic or oligodendrocytic series. Each example yielded results higher than any of the other well differentiated gliomas, and no difference was found between a well differentiated example and 2 overtly malignant ependymomas. The choroid plexus papilloma constitutes a special item of consideration since, despite its completely benign morphologic appearance, its enzyme activity on 11 determinations was among the highest of the entire series (Fig. 8). In view of the fact that the tumor was composed of papillae containing loose connective tissue cores and that in some areas an abundance of a colloidal secretory material found to be mucoprotein was present, the possibility existed that these 2 tissue components might conceivably contribute in a major way to the high enzyme activity. In an effort to shed some light on this problem, the volumes per cent of connective tissue and of mucoprotein were estimated by the method of histologic quantification already described. The results are plotted in Figure 9 together with the individual values of beta-glucuronidase for each set of the serially sectioned frozen block. It will be seen that the enzyme activities show some initial variations but with highest values being reached in the deepest third. The quantity of connective tissue is highest in the initial and middle portions of the block, dropping in deeper layers. The amount of mucoprotein rises from an almost negligible amount in the first half to appreciable levels approaching 16% in the last half. Although the irregular variations in these quantities preclude any highly detailed analysis of individual tissue contributions, it is nevertheless clear that no major enzyme activity may be attributed to the mucoprotein nor does the curve of quantity of connective tissue in any way follow that of total enzyme activity. Therefore, it appears reasonable to assume that the loose connective tissue cores of the papilla are not the sole or major source of enzyme but rather that the neoplastic epithelium itself must make a principal contribution. With the exceedingly high enzyme activities obtained, this neoplastic choroidal epithelium occupies an unique position in regard to well differentiated neoplasms of other cell races of the nervous system.

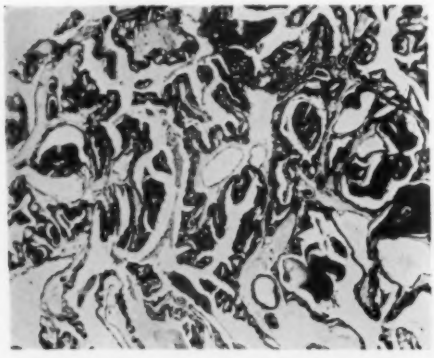

Fig. 8. T-30. Choroid plexus papilloma with dense staining colloidal material between folds of papillae. Periodic acid–Schiff. × 75

Some other primary malignant tumors in nervous tissue included a medulloblastoma, a peripheral neuroblastoma, and a fibrosarcoma of brain existing as a mixed tumor with a glioblastoma multiforme.[16,17] The sample herein reported as fibrosarcoma consisted predominantly of this component of the tumor with but minimal fragments corresponding to the glioblastoma multiforme. All 3 of these tumors showed activities greater than normal brain or pia-arachnoid and greater than the well differentiated astrocytic and oligodendrocytic tumors. All were within the range noted for the class glioblastoma multiforme, and

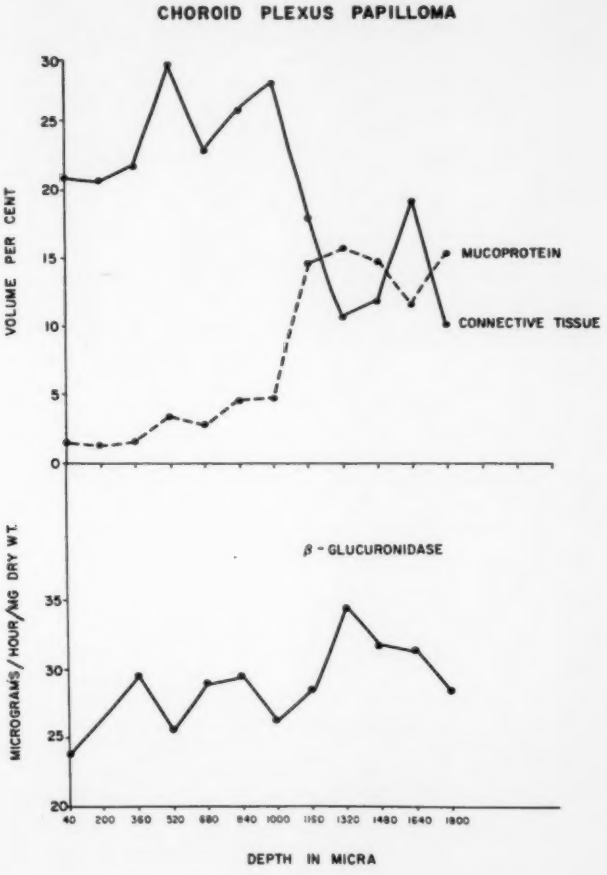

Fig. 9. Serial sections at 40 μ were carried out on a sample of choroid plexus papilloma with beta-glucuronidase determination and histologic analysis at each level. Volumes of connective tissue and mucoprotein were estimated as described in the text.

the medulloblastoma and neuroblastoma were within that more narrow range noted for ependymomas.

Both benign tumors designated as schwannoma, 1 from spinal nerve root and 1 from the eighth nerve, corresponded to Antoni's type A variant of this tumor. Activity of beta-glucuronidase was much higher than values obtained in normal brain or pia-arachnoid and in well differentiated astrocytoma and oligodendroglioma.

Of 4 meningeal tumors studied, 3 were characteristic cellular meningothelial meningiomas with varying numbers of whorls. Each of these tumors has yielded amazingly similar values, so close, in fact, that one must wonder if an astonishing coincidence were not at play. Nonetheless, it must be noted that the single meningeal tumor departing from this characteristic and being essentially a meningeal hemiangioblastoma (angioblastic meningioma) had less than half the activity of any of the other meningiomas and without any overlap of individual determinations (Figs. 10 and 11).

For comparison, 3 secondary tumors are listed. The values found for the metastatic breast carcinoma and the metastatic melanoma are compatible with those reported by others for primary tumors of this type.[4]

Necrosis. In Table 1 are listed 2 examples

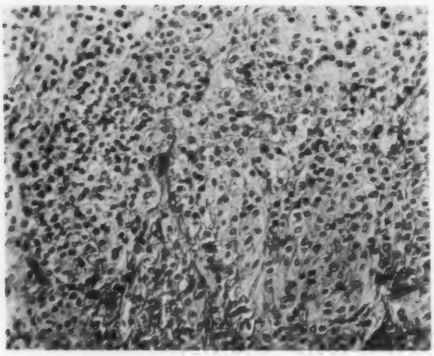

Fig. 10. T-45. Angioblastic meningioma, showing sheets of cells with clear and foamy cytoplasm. Hematoxylin and eosin. × 200

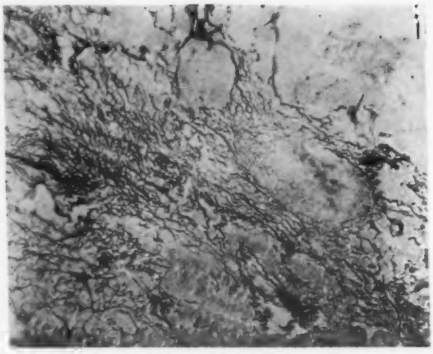

Fig. 11. T-45. Angioblastic meningioma, showing abundant production of reticulin by tumor cells. Perdrau. × 75

of total necrosis existing in glioblastoma multiforme. It is of considerable interest that, unlike cytochrome oxidase[1] and dehydropeptidase I,[2] beta-glucuronidase survives in abundance. It must be noted, however, that in each example of necrotic material the level of activity in necrotic portions was much less than in the viable portions of the respective tumor.

Abscess wall. Although of little relevance to the question of biochemical characteristics of neoplasia, a single abscess wall was studied in view of the possibility that its strikingly laminated structure might yield information upon the range of beta-glucuronidase activity to be seen in diseased brain and upon the role played by invading leukocytes and fibroblasts. Accordingly, a frozen cylinder of tissue was prepared at an angle perpendicular to the inner surface of the abscess wall and so mounted that the initial sections were obtained from the purulent surface. Serial sectioning was continued for a depth of almost 3 mm. with 19 sets of determinations obtained. The initial set was composed of necrotic debris and polymorphonuclear leukocytes. The next sets contained great numbers of polymorphonuclear leukocytes and with increasing amounts of loose granulation tissue. In deeper layers, polymorphonuclears decreased while clumps of plasma cells and scattered lymphocytes appeared. Only in the last 1 or 2 sets were scattered astrocytes seen. It was possible to quantitate by methods already mentioned the numbers of polymorphonuclear leukocytes within each control section. Fibroblasts and endothelial cells were counted together. Undoubtedly, a few astrocytes were counted with these in the deepest sets, but the number of astrocytes present was sufficiently low as to make no significant error. The numbers of the respective cells as well as beta-glucuronidase activities are charted in Figure 12. Beta-glucuronidase attains a peak level of 33.8 units at a depth of 240 μ followed by a steady decline to a plateau level ranging between about 6 and 8 units. The polymorphonuclear count follows the beta-glucuronidase curve rather closely and is indeed the only cellular element which can account for the initial peak levels. The next most abundant group of cells in the more superficial layers, fibroblasts and endothelial cells, clearly cannot account for the curve of enzyme activity. After the polymorphonuclear population declines to almost negligible levels in the deepest layers, the residual beta-glucuronidase activity must be due to a combined contribution of the remaining inflammatory cells, fibroblasts, and a few astrocytes. The fact that beta-glucuronidase activity is lower at the depth of 80 μ than at the depth of 240 μ is attributed to the fact that the initial set involved a section containing only polymorphonuclears and necrotic debris, being deprived of the contribution of those other viable tissue elements found deeper in the section.

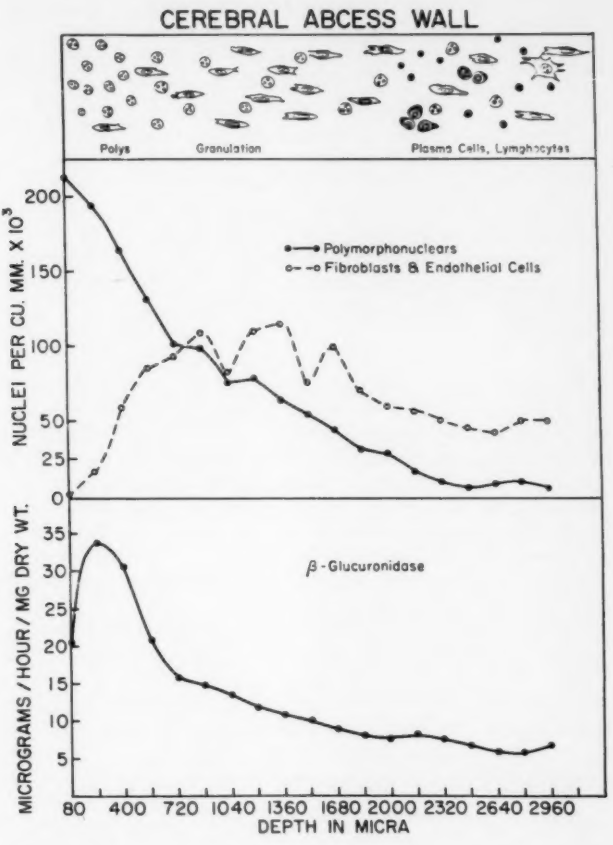

Fig. 12. Serial sectioning was carried out on a cerebral abscess wall to a depth of almost 3 mm. At each level, beta-glucuronidase was measured and cell counts made of the major cellular components. A necrotic exudate was confined to the set at 80 μ.

Qualitative histochemistry. In Table 2, the varying beta-glucuronidase activities of 6 tumors of various degrees of dedifferentiation are compared with the intensity of Seligman's[5] method of staining of adjacent blocks of the respective tumors. Under this method, 6-bromo-2-naphthol is liberated by the enzyme in tissue section and is subsequently colored with a diazo compound to produce a blue color. The intensity of stain was rated visually on a scale of 0 to 4 by comparison with stained rat tissues of predetermined enzyme activities. In Table 2, the tumors are arranged in descending order depending upon the intensity of stain. Beta-glucuronidase activities by our own quantitative determinations are indicated in the middle column. It will be seen that there is a rough correlation of intensity of stain with the quantitative determination. There are 2 exceptions, however, the most striking being specimen T-64, which has the highest value of the group but a stain intensity of only 3.

DISCUSSION

From the foregoing data, it may be concluded that some argument can be presented for distinctive distribution patterns of beta-glucuronidase activity in several groups of tissues: the enzyme is low in cerebrum as a whole but higher in white matter than in cortex, is lower in well differentiated astrocytomas and oligodendrogliomas than in any other tumors in the group, has a wide range of high activities in the glioblastomas and with

TABLE 2
COMPARISON OF QUANTITATIVE AND QUALITATIVE ESTIMATIONS OF BETA-GLUCURONIDASE ACTIVITY

Tissue			Activity (μg. per hour per mg. of dry weight)	Intensity of stain (Seligman's method)
Glioblastoma multiforme	(3)*	T-56	12.77	4
Ependymoma, malignant	(4)	T-40	12.71	4
Glioblastoma multiforme	(3)	T-64	14.3	3
Glioblastoma multiforme	(3)	T-36	6.73	3
Glioblastoma multiforme	(3)	T-55	7.50	2+
Astrocytoma, anaplastic	(2)	T-33	3.29	2

*Numeral in parentheses refers to grading by Kernohan's system.

some possibility of subdivision according to histologic type, and is of moderately high activity in the group of ependymal tumors. Of even more interest would be a knowledge of the role of this enzyme in cellular metabolism and of the biochemical significance of the considerable variations among the several specimens. Thus far, an enormous volume of data has accumulated on the distribution and properties of beta-glucuronidase, and many interesting hypotheses concerning its action have been put forward. Nevertheless, it must be said that at the present its function in vivo has yet to be clearly elucidated.

The enzyme has an ubiquitous distribution, being present in all tissues of the animal body and in microorganisms.[3] In mammals, it is present in greatest activity in spleen, then liver and endocrine tissues.[3] Some evidence has been advanced for the existence of 3 separate enzymes existing in spleen and liver and differentiated by different *p*H optima.[18,19] However, this point has been seriously questioned and remains unlikely.[3] Some differences in substrate utilization have been demonstrated with preparations of the enzyme from different sources; however, there has been found in all the consistent property of catalyzing hydrolysis of a wide variety of glucuronides having the beta-glucuronosidic linkage. This hydrolytic function of the enzyme has been demonstrated for a great variety of aglycones including phenols, phenolphthalein, menthol, borneol, alcohols, and steroids, all of which can be demonstrated to undergo glucuronide conjugation upon administration to animals. Of perhaps greater interest is the ability of beta-glucuronidase to hydrolyze glucuronides important to normal intermediary metabolism. This group includes the glucuronides of steroids and other hormones[3] and the glucuronide containing oligosaccharide fragments of hyaluronic acid.[20]

Function of beta-glucuronidase. The relationship of beta-glucuronidase activity to certain steroid hormone effects led Fishman[3] to consider that the enzyme was directly concerned with the metabolism of these hormones in certain target organs. Thus, the estrogen-induced endometrial proliferation in castrated mice was associated with a marked rise in beta-glucuronidase activity.[21] Similarly, the renotrophic action of androgens was also attended by a striking elevation in renal beta-glucuronidase.[22] It was Fishman's contention that the enzyme in these tissues played a role in the liberation and utilization of the glucuronide-bound hormone and that its increase during stimulation was essentially an adaptive one. While such a specific role may exist, it seems clear that this could account for but a small fraction of the more general function of beta-glucuronidase in the animal body.

Beta-glucuronidase has been considered a function of growth and cell division, and indeed its usually high activities in tumors have been attributed to such a relationship.[23] Numerous exceptions have been shown for such a generalization, however, since not all growth is accompanied by a rise in enzyme activity nor does the elevated activity, if it is present, coincide with the peak of cell proliferation, as measured in regenerating liver[24] or wallerian degeneration.[25] Furthermore, not all tumors

show high enzyme levels, as attested by the experimental hepatoma in rat.[26]

A role in the synthesis of glucuronides has been argued by Fishman,[3] but to date no proof has been advanced for synthetic action, and the currently accepted concept of glucuronide synthesis allows no place for beta-glucuronidase.[27] Of more interest is the possibility of a participation in glucuronide transfer. Fishman[11] has demonstrated the in vitro transfer, in high yield, of glucuronyl group from several aglycones to a variety of alcohols. It remains a possibility that an in vivo transferase reaction, somewhat akin to transpeptidation, may occur.

After the demonstration by Meyer, Linker, and Rapport[20] that partly purified beta-glucuronidase preparations could continue the hydrolysis of oligosaccharides released from hyaluronic acid by hyaluronidase, it was contended that beta-glucuronidase might play some role in the turnover of glucuronide containing acid mucopolysaccharides.[23] Bollet, Goodwin, and Brown[28] also advanced an hypothesis that the enzyme might participate in mucopolysaccharide metabolism after finding activities of beta-glucuronidase as well as members of the glucuronide synthesizing chain in experimental granulomas in guinea pig.

Of particular importance have been the recent investigations of de Duve and his associates,[29,30] who have produced evidence for the existence of a new class of subcellular particles containing beta-glucuronidase and other hydrolytic enzymes having acid *p*H optima. Using a refined centrifugation technic, these investigators found a common sedimentation pattern for the enzymes beta-glucuronidase, cathepsin, acid phosphatase, acid ribonuclease, acid desoxyribonuclease, and aryl sulphatase. It is postulated that a subcellular particle, the lysosome, contains these enzymes in a bound state in relative isolation from the cytoplasm. Tentative electron microscopic studies of these particles seem to identify them as dense granules, probably the same as those previously designated as pericanalicular dense bodies, siderosomes, and residual bodies.[31] De Duve[32] suggests that the lysosome enzymes may participate in processes involving the intracellular engulfment of some large molecular substances, as in the processes of phagocytosis and pinocytosis. Regressive processes and necrosis may result in the release of bound lysosomal enzymes for active digestion of the cell. Van Lancker and Holtzer[33] have demonstrated such a release of beta-glucuronidase in autolyzing mouse liver.

The data presented here lead to no new insights as to function of this enzyme in cellular metabolism, but they do support some of the existing hypotheses and permit certain conclusions regarding the enzyme distribution in some cell types and in some pathologic processes within the nervous system.

Relation to necrosis. Firstly, it may be pointed out that total (representing free plus bound) enzyme persists at high levels within areas of complete necrosis in a glioma. The enzyme is therefore not destroyed, at least in early stages of necrosis, as are some other enzymes such as cytochrome oxidase[1] and dehydropeptidase I.[2] Presumably, the enzyme remains active in such areas, doubtless at a slightly acid *p*H, and plays a role in the hydrolysis of some products of cellular breakdown just as it may in the autolyzing preparations of mouse liver.

Phagocytosis. Another evident role of high enzyme activity in one of our specimens is in relation to the process of phagocytosis. It was noted that very high activities in the inner layers of an abscess wall could be correlated with the numbers of polymorphonuclears present, a source of no great amazement in view of the demonstration by Rossiter and Wong[34,35] of quite large activities of enzyme within rabbit and human polymorphonuclears. A number of compounds in the nervous system could be the source, upon molecular breakdown, of oligosaccharides containing a beta-glucuronide linkage. Acid mucopolysaccharides, as one such possible source, have been identified in brain[36] and axoplasm.[37] If such are indeed liberated and require hydrolysis in encephalomalacia, one might expect phagocytes of a more chronic process, the compound granular cells, to be involved. Thus far, no satisfactory specimen containing such cells has reached our hands for direct measurement of beta-glucuronidase. Some indirect evidence was obtained by the assay of samples of spinal fluid for enzyme, in a case of necrotizing myelopathy of unknown cause. During a time in which spinal fluid activity for beta-glucu-

ronidase reached a level of 10 times that of the mean normal, biopsy of the softened cord showed complete loss of architecture and replacement by compound granular cells.

It appears reasonably certain then that polymorphonuclears in active phagocytosis within brain tissue produce high beta-glucuronidase activities and quite probable that compound granular cells do the same. In the light of these data, one wonders if the finding by Hollinger and Rossiter[25] of a great elevation of beta-glucuronidase activity in distal segment of sectioned nerve reaching a peak at the sixteenth day might not be related in part to phagocytes. This peak occurred after the estimated peak in Schwann cell proliferation, although these cells must make at least a partial contribution to the total enzyme. However, as Ramón y Cajal[38] points out in the rabbit at least, active phagocytosis becomes very striking by the eighteenth day and might very well continue to influence beta-glucuronidase content after the initial proliferative phase.

Relation to metabolic properties of nervous tissues. Neither necrosis nor phagocytes could account for the distribution patterns of the enzymes in the tumor series, subjected as it was to careful histologic control. Of course, it might be argued that malignant glial cells, hovering between relentless growth on the one hand and imminent cell death and dissolution on the other, could well be richly endowed with lysosomal hydrolytic enzymes for the catabolism of the decaying cells or quite possibly for some intracellular "physiologic autolysis," the purpose of which is as yet undefined. Yet, one must conclude that consistent differences in enzyme activity of well differentiated tumors of some cell lineages (ependymal) as opposed to others (astrocytic and oligodendrocytic) must represent a basic difference in the metabolism of viable cells of the respective series. The basic function reflected by such differences continues to elude us. Concerned with the possibility of a role of beta-glucuronidase in the metabolism of acid mucopolysaccharides, we stained a group of the specimens using contemporary methods for proteins, acid mucopolysaccharides, lipids, and mucoproteins. While the full results are not the subject of the present report, it is appropriate to state that, although acid mucopolysaccharides and mucoproteins may be demonstrated in some gliomas, no correlation was found between the presence of acid mucopolysaccharide and level of beta-glucuronidase activity. Of particular interest was the choroid plexus papilloma, where the presence of extraordinary enzyme activities as well as equally remarkable quantities of secretory material between papillae and within cytoplasm, suggested a possible dependent relationship between the two. Histochemical staining methods did reveal a small amount of acid mucopolysaccharide within the loose connective tissue cores, but the abundant secretory material proved to have the characteristics of mucoprotein. No positive evidence has, therefore, been obtained supporting the hypothesis that beta-glucuronidase is concerned in the turnover of acid mucopolysaccharides.

In regard to the major question of biochemical description of the varieties of nervous system tumors, one may discern distribution patterns of beta-glucuronidase appearing to be characteristic for some of the histologically benign nervous system tumors. Thus, well differentiated astrocytomas and the oligodendroglioma were quite low in enzyme activity, whereas the tumor of choroid plexus was exceedingly high and a well differentiated ependymoma occupied an intermediate position. The 2 benign schwannomas also occupied an intermediate position; 3 meningothelial meningiomas showed remarkably similar mean values at about 7 μg. per hour per milligram of dry weight, whereas the single angioblastic meningioma had less than half this activity. In previous studies of some enzymes in nervous system tumors,[1,2] the conclusion had been reached that activities in well differentiated tumors may closely reflect the corresponding enzymic composition of the normal cell of origin. Data with which to judge such a relationship for beta-glucuronidase are thus far quite incomplete. It is apparent, however, from the quite low enzyme activity within white matter as compared to other tissues that beta-glucuronidase activity within normal astrocytes or oligodendrocytes must be low. This appears to be in general agreement with the fact that the enzyme activity was low in the well differentiated astrocytomas and oligodendroglioma in comparison to the rest of the

tumor group. The relationship does not appear to hold for the meningiomas, the values of which were much higher than that of the normal pia-arachnoid.

Anaplasia. It could be argued that beta-glucuronidase may serve as something of an index to the presence of malignant change in tumors. No such relationship is found in the present group of tumors. That is to say, one does not find low beta-glucuronidase activities in all benign tumors and high activities in all malignant tumors. One need only point out, for example, that the medulloblastoma was lower in activity than was the ependymoma or one of the schwannomas. On the other hand, the choroid plexus papilloma was the second highest of any of the primary nervous system tumors. This tumor was unequivocally benign by morphologic characteristics. The subject, a patient of the author, had experienced symptoms attributable to the mass for four years before admission. At operation, the mass was large but well circumscribed and removed in toto. After an operative death, postmortem examination revealed no residual tumor nor any evidence of seeding within meninges over the cerebrum or the spinal cord. No over-all relationship, therefore, may be adduced for relation of beta-glucuronidase content to the malignant state as such.

Within tumors of an individual cell line, however, there is some possibility of relating beta-glucuronidase activities to the degree of anaplasia. The most complete data would be for the tumors of astrocytic derivation. In those tumors composed either totally or predominantly of cells having well differentiated form, activities were always low. Within the group of glioblastoma multiforme, most of which in the present series contain cells having characteristics of astrocytes, the level of enzyme activity appears to be related to increasing anaplasia. All of these tumors showed the classic characteristics of vascular hyperplasia, mitoses, giant cell formation, and pseudopalisading about focal necrosis. Some of the tumors, however, were composed predominantly of cells having good uniformity and clearly reproducing characteristics of astrocytes; 2 examples of this would be T-55 with a principally protoplasmic form and T-28 with a dominant pilocytic form. Such tumors have activities in the lowest range of the glioblastoma group. Tumors which are clearly more anaplastic, conforming perhaps to the average or common glioblastoma multiforme tumors and particularly those with plump gemistocytic cells, all have activities in a higher range. Finally, when one comes to such grossly anaplastic tumors as T-51, the giant cell inclusion body glioblastoma, where no recognizable astrocytic forms are identified, beta-glucuronidase attains maximal activity. The juvenile pilocytic cerebellar astrocytoma (T-64) may occupy a somewhat special niche. Although we were well aware of the great rarity of malignant astrocytoma of the cerebellum and of the special cytologic interpretations of Russell and Rubinstein[12] within the group of cerebellar astrocytomas, the characteristics of pleomorphism, giant cell formation, and vascular hyperplasia in many areas of the tumor led us to consider these parts malignant and conforming to glioblastoma multiforme, whereas other areas were not evidently malignant but were composed of pilocytic astrocytes whose cell density and mild pleomorphism connoted only moderate anaplasia. Within these latter more well differentiated areas, beta-glucuronidase activities fell into a midzone between the well differentiated astrocytomas and the glioblastoma group. The levels of activity on 2 such specimens were clearly different from those obtained on a very well differentiated fibrillary cerebellar astrocytoma from an adult. When serial sections obtained from the better differentiated pilocytic portion of T-64 gradually entered the areas considered as glioblastoma, it was always found that beta-glucuronidase activity gradually rose to reach that level quoted as a mean figure after T-64 C as 14.3 units. Thus, a general tendency is seen for increasing beta-glucuronidase activities to accompany increasing anaplasia within the astrocytic series. Very little may be said for the oligodendrocytic series, since no malignant tumors composed predominantly of cells resembling oligodendrocytes were obtained. Only T-43, a mixed glial tumor composed in part of cells having oligodendrocytic characteristics, was included, and this tumor did show levels of enzyme activity very much greater than the well differentiated oligoden-

droglioma and corresponding to other examples of glioblastoma multiforme. For the ependymal series of glial tumors, there is no relationship to anaplasia whatsoever.

In view of this relationship of beta-glucuronidase to anaplasia within the astrocytic group, the tumors were graded according to the criteria of Kernohan[14] and arranged in Table 3 under grades 1 through 4. The mean figures from each group follow a startlingly close adherence to a straight line relationship with the grade. We hasten to point out, however, that this striking relationship is in part artifactual and is subject to numerous exceptions among individuals. Within grade 2, for example, the mean figure of 5.03 is attributable entirely to the contribution of the single cerebellar astrocytoma. Within grade 3, tumor T-24 has a value of 25.7, being higher than the mean figure for grade 4. Although some general relationship to increasing anaplasia is evident, it would seem much more preferable to state simply that astrocytic tumors having quite well differentiated cells are liable to have low activities whereas those with poorly differentiated cells will be higher.

A particular departure of level of beta-glucuronidase activity from the grading system concerns the failure of higher activities to be found among most of the anaplastic astrocytomas (grade 2) as compared to the well differentiated tumors. The particular examples in mind include specimens T-25, T-33, and T-58, all of which fell well within the range of the well differentiated astrocytomas. It must be concluded from this that, in respect to this one enzyme at least, a subtle enzymatic change in the direction of malignancy need not occur generally throughout a tumor shown to be focally disposed to such a change. The relatively low activities are attributed to the fact that the great majority of cells present in the analyzed specimen were well differentiated in form. If indeed little clusters of pleomorphic cells or of cells in a focally dense perivascular arrangement had developed high beta-glucuronidase activity, such focal contributions were doubtless submerged beneath the numerical superiority of well differentiated cells comprising the specimen.

Qualitative histochemistry. In such an endeavor as the study of enzymes in brain tumors where many difficulties are always present, it is often useful to have available an additional technic of study in order to lend added verisimilitude to an already well tested approach. With this purpose in mind, the qualitative histochemical method of Seligman[5] was utilized in some of the specimens as well as in samples of many rat tissues. There are some considerable reservations about the application of this technic to the study of the normal nervous system in view of differing distribution obtained in brain with the use of another technic[39] and because of some selective tissue affinity of the product of hydrolysis noted by us. Nevertheless, the over-all color density of sections from various rat organs stained by Seligman's method compares favorably with our own quantitative results. Consequently, we did subject a number of tumors to the histochemical staining reaction comparing the results with those obtained by the quantitative method upon nearby blocks from the same specimen. A rough grading of the density of over-all color was performed using the color intensity of rat tissues of known enzymatic activity as a scale of reference and rating intensity from 0 to 4 (Table 3).

Some general correlation between the 2 methods is readily apparent since most of those tumors with high activities produced a definitely more intense stain than did that specimen of lowest activity. More detailed attempt at correlation revealed 2 exceptions. T-64, for example, while having an intensity of 3^+, nevertheless was the highest in activity of the group. We may therefore only note a rough but not a precise correlation between the 2 technics, recognizing, however, that the 2 methods were carried out on adjacent blocks rather than on alternating sections. While the results on certain rat tissues indicated the possibility of excessive affinity for the liberated 6-bromo-2-naphthol of myelin lipids of peripheral nerve and the surfaces of adipose tissue cells, it is noted that this is an error of a false-positive sort and no evidence has been brought forward at present to indicate any serious defects of a false-negative type. Consequently, the method was applied to the staining of a number of specimens of glioblastoma multiforme in an effort to determine whether the vascular hyperplasia present in

most of these samples could account for some of the high enzyme activities found in them. The Seligman stain did not reveal any intense staining of areas of vascular hyperplasia but rather revealed the most intense stain to be confined to areas of glial tumor cells. The abnormal blood vessels either stained lightly or not at all, and in no case did they approach in depth the coloration of surrounding tumor. This observation, then, stands in agreement with the quantitative observations which indicated that, in serial sections of a given tumor in which certain sets contained a significantly greater proportion of vascular hyperplasia than others, no change in over-all enzyme activity appeared.

SUMMARY

The use of a quantitative histochemical technic requiring as little as 10 μg. of dry weight of tissue sample has proved quite satisfactory for the study of beta-glucuronidase activity in a series containing examples of the major varieties of nervous system tumors. Although all malignant tumors yielded values much higher than those obtained from normal

TABLE 3

RELATIONSHIP OF BETA-GLUCURONIDASE TO A SYSTEM OF GRADING FOR ASTROCYTOMAS (KERNOHAN)

		Beta-glucuronidase (*μg. per hour per mg. of dry weight*)
GRADE 1		
T-27	Astrocytoma, fibrillary, diffuse	4.08
T-32	Astrocytoma, fibrillary, cerebellar	1.10
T-29	Astrocytoma, protoplasmic	1.71
T-66	Astrocytoma, protoplasmic	4.68
		Mean 2.89
GRADE 2		
T-25	Astrocytoma, anaplastic	2.87
T-33	Astrocytoma, anaplastic	3.29
T-58	Astrocytoma-oligodendroglioma, anaplastic	4.37
T-64	Astrocytoma, juvenile pilocytic, cerebellar	8.01 6.6
		Mean 5.03
GRADE 3		
T-24	Glioblastoma multiforme, gemistocytic	25.7
T-28	Glioblastoma multiforme, pilocytic	10.08
T-23	Glioblastoma multiforme, gemistocytic	14.55
T-36	Glioblastoma multiforme, spindle cell	6.73
T-55	Glioblastoma multiforme, protoplasmic	7.50
T-56	Glioblastoma multiforme, gemistocytic	12.77
T-64	Glioblastoma multiforme, cerebellar	14.3
		Mean 9.79
GRADE 4		
T-37	Glioblastoma multiforme, astroblastic	16.25
T-43	Glioblastoma multiforme, mixed	21.4
T-51	Glioblastoma multiforme, giant cell inclusion	32.7
T-59	Glioblastoma multiforme, gemistocytic	15.3
		Mean 21.41

cortex or subcortical white matter of frontal lobe, no relationship could be attributed to the presence of malignant tissue per se since a number of clearly benign tumors showed higher values than certain malignant specimens. The most striking correlations have been in regard to the several cell lines of neoplasms and, in the case of astrocytic tumors, to the extent of anaplasia within the group. Among the group of tumors of ependymal origin, all examples showed moderately high activity regardless of the degree of differentiation. As a special example of this group, a choroid plexus papilloma yielded one of the highest values in the series, a finding which is believed to reflect a special enzymatic property of the choroidal epithelium. Well differentiated tumors of the astrocytic and oligodendrocytic series had quite low values among the tumor group as a whole. Most anaplastic astrocytomas were not different from well differentiated forms. The glioblastoma multiforme group, most of which had some astrocytic characteristics, showed enzyme activities much greater than the well differentiated astrocytomas. Within the glioblastoma group, those with fairly well differentiated cells showed lower activities than those which were distinctly more anaplastic.

Total beta-glucuronidase activity persists in areas of complete necrosis within malignant glial tumors but does not attain as high a level as in the corresponding viable tissue. Within an abscess wall, some very high levels found in the inner layers could be correlated with the presence of polymorphonuclear leukocytes.

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A brain stem lesion of unusual etiology

A case report

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AT THE TIME of the patient's final admission, a presumptive diagnosis of posterior inferior cerebellar artery syndrome was made. The lateral medullary or Wallenberg[1] syndrome, due to occlusion of the posterior inferior cerebellar artery, is a complex of signs consisting of ipsilateral loss of pain and temperature sensations of the face, Horner's syndrome, nystagmus, dysphonia, and dysphagia and contralateral loss of pain and temperature sensations of the trunk and extremities, often associated with weakness. Also, there may be homolateral cerebellar dysfunction of the arm or leg, facial muscle paralysis, and hearing loss.[2] The syndrome is most common in hypertensive men over the age of 40,[3,4] and the prognosis is poor.[5] Arteriosclerotic thrombosis is considered to be the most common etiologic factor, although arteritis, aneurysm, syphilis, and polycythemia vera also have been implicated.[3] The present case is reported because of the unusual etiology and the failure to diagnose the lesion despite usual laboratory and contrast studies.

CASE REPORT

A 36-year-old man was admitted to the hospital on October 8, 1959, from a hospital in France, with a diagnosis of cerebrovascular accident. While standing on retreat parade September 11, he noted a roaring in his ears, immediately followed by dizziness and numbness of the left face and right arm and leg. He was asymptomatic within seven hours except for mild residual extremity numbness. Ear, nose, throat, and spinal fluid examinations were normal. On September 15, he experienced similar symptoms lasting ten minutes and again on September 27 with persistence of symptoms. He was hospitalized September 29 and transferred to the Second General Hospital in Germany with his condition unchanged.

The past history revealed that a malignant melanoma was removed by wide excision from the right scapular area on February 23, 1955. On March 11, 1955, a radical in-continuity dissection of the skin, fascia, and lymphatics of the right axilla was performed. This tissue was examined, and no evidence of malignancy was found. In 1957, he was treated for four months for a gastric ulcer which was demonstrated on 3 separate gastrointestinal radiologic examinations.

Physical examination showed the patient to be a lucid, well developed white man who did not appear chronically ill. A hard, cherry-sized node was palpated deep in the left sternocleidomastoid muscle; a healed right lower quadrant (appendectomy) scar and right back and axillary scars were noted. Neurologic examination revealed horizontal nystagmus most active when he looked to the left, diplopia on left lateral gaze with the false image more laterally displaced and seen with the left eye, left lower facial paresis, weak gag reflex, and impairment of pain and temperature sense of the left lower face and the right side of the trunk and extremities. On admission, there was no incoordination or ataxia, but he felt a tendency to fall to the left during the Romberg test. No Horner's signs nor palate paralysis was observed.

The routine blood and laboratory examina-

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tions were within normal limits. The total protein was 5.1 gm. per cent, with a 1.6:1.0 albumin to globulin ratio. Spinal fluid examination revealed no cells, 18 mg. per cent of protein, nonreactive serology, and an "all-zero" colloidal gold curve. Towne and Stenver views of the petrous bones, 2 skull radiologic examinations, and chest roentgenograms were negative. On October 16, a pneumoencephalogram was performed and proved normal. A right vertebral arteriogram was done on October 21. The right vertebral and basilar arteries filled normally. There was slight reflux filling of the left vertebral; the left posterior inferior cerebellar filled for only 1 cm.

On October 10, the patient had another severe episode of dizziness and weakness with nausea and vomiting. Subsequently, he remained weak and had repeated similar attacks, especially while attempting deglutition. His inanition necessitated intravenous feedings on October 17. Four days later, conjugate gaze was impaired and warfarin anticoagulation therapy was begun. A prothrombin control level between 20 and 30% of normal was maintained until the day before his death, when it was allowed to rise. On October 27, in addition to his progressive weakness and sensory loss, his temperature rose and he became deaf in the left ear. Three days later, Cheyne-Stokes respiration developed and the patient died.

The gross necropsy findings revealed blood in the subarachnoid space and a large area of encephalomalacia in the centrum ovale of both frontal lobes. In the right frontal lobe was a $1.3 \times 2 \times 3$ cm. hemorrhagic cystic area extending to within 1 cm. of the tip of the frontal lobe. The entire left side of the brain stem, from the level of the motor nucleus of the hypoglossal nerve to the level of the midbrain, was occupied by hemorrhagic and necrotic tissue which extended into the ventral portion of the cerebellum. The hemorrhage and edema had obviously encroached upon and distorted the right side of the medulla. Both lungs were congested and showed evidence of bronchopneumonia.

Microscopically,* melanoma cells were found in several peritoneal and cervical lymph nodes and in one area of periadrenal adipose tissue. Metastatic melanoma cells were found in the hemorrhagic area of the right frontal lobe and in the brain stem at the level of the pons. These tumor cells were abundant in the necrotic tissue encountered on gross examination (Figs. 1 through 3).

*The microscopic evaluation was done by Lt. Col. J. M. Lukeman, M.C., to whom the authors are also indebted for technical assistance.

CASE DISCUSSION

The sudden onset of the patient's illness, with transient dizziness and numbness of the left side of the face and right side of the body on two occasions, followed in a few days by recurrence with persistent symptoms, suggested left posterior inferior cerebellar artery thrombosis. The neurologic examination revealed, in addition to the classic signs of a Wallenberg syndrome, ipsilateral involvement of the sixth and seventh cranial nerves. This finding suggested an extensive brain stem lesion. Furthermore, the past history of malignant melanoma indicated that a metastatic lesion in the brain stem must be ruled out. During the first two weeks, spinal puncture, electroencephalogram, chest and skull roentgenograms, pneumoencephalogram, and vertebral arteriogram were negative. Because of the patient's gradual downhill course and the lack of confirmation of a metastatic lesion, anticoagulation was started. Despite the control of the prothrombin level at 25%, the patient began to fail rapidly and further evidence of brain stem involvement was noted. Three weeks after admission, the patient lapsed into coma and died. The hemorrhagic areas encountered at autopsy could not be attributed to anticoagulant therapy because of the frequency of hemorrhage in metastatic melanoma[6] and the accurate control of the prothrombin level.

COMMENT

About 20% of cerebral neoplasms are metastatic, and only 6% of these originate from the skin.[6] Malignant melanoma has an annual incidence of about 1.8 per 100,000,[7] and nearly one-half of these metastasize to the brain.[8] Hence, malignant melanoma is not common, and studies which accurately describe the number and location of metastases within the central nervous system are wanting.

In a report of 5 autopsied cases with cerebral metastases, all brains contained multiple metastases, with the frontal and occipital lobes most often involved.[9]

Perhaps the most interesting feature of this neoplasm is its latency, amply exemplified by this case. Wilber and Hartman[10] have commented: "There are few conditions apparently so readily cured in certain cases by simple excision as in the melanoepithelioma, only to recur many years later with a rapidly fatal form following an interval of perfect health." Twenty or more years have been known to elapse between discovery of the primary malignant lesion and death.[11,12] Reasons hypothesized for the delayed metastatic growth are lowered organ resistance, increased aggressiveness of tumor cells,[10] and immunologic factors.[13] Apparently, hormones influence the activity of melanomas, since pregnancy and puberty have been known to induce grossly malignant changes,[7,14,15] and malignant melanoma is unknown in castrates.[16]

Five-year cure rates are improving, probably the result of early definitive surgery. In a series ending in 1945, Pack, Gerber, and Scharnagel[15] report 26 to 27% survival; more recently, Lane, Lattes, and Malm[17] report 34.3% and Daland,[18] 52.3%. The size of the initial lesion and involvement of the regional lymph nodes seem to materially influence the prognosis. Lane and associates[17] report a five-year cure in 61% of their cases if the lesion is less than 2 cm. in diameter, as opposed to 16% if the lesion exceeds 2 cm. Pack and associates[15] show a five-year cure in 40.5% if, at surgery, the regional nodes are uninvolved and 14.1% if they are. It is of interest that a delay of more than four weeks before definitive surgery after original resection may decrease five-year cure rates from 39.9 to 17%.[15] Our patient had definitive surgery sixteen days after the original resection and was asymptomatic more than five years.

This latent period and cerebral metastases from unsuspected primary growths have caused many diagnostic errors.[19,20] Metastatic melanoma should be included in the differential diagnosis if a patient has had a suspect dermal lesion and shows signs of intracranial pathology, regardless of the intervening time lapse.

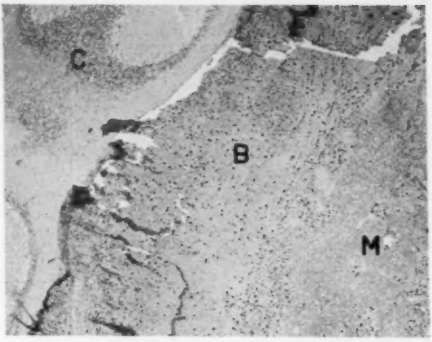

Fig. 1. C=folia of normal cerebellum. B=organized blood clot. M=malignant melanoma. × 15

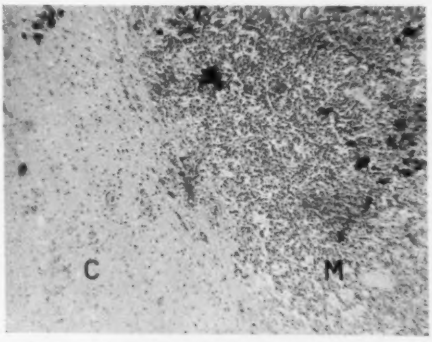

Fig. 2. M=malignant melanoma cells invading normal cerebral tissue (C). × 50

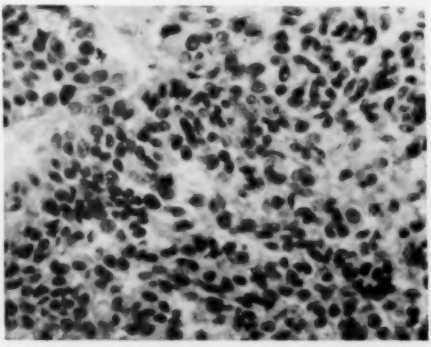

Fig. 3. Metastatic melanoma in brain tissue. Note pleomorphism and pigmentation of cells. × 300

SUMMARY

1. A case of metastatic melanoma presenting as a vascular lesion of the brain stem is reported.

2. The unusual features of the latency period of metastatic melanoma are discussed.

3. Factors influencing the prognosis in malignant melanoma are reviewed.

This material has been reviewed by the Office of the Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

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Use of anticoagulants in patients with progressive cerebral infarction

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In view of the conflict of medical opinion concerning the value and dangers of anticoagulant therapy in patients with cerebral infarction, it is necessary to attempt an assessment of this problem by clinical trial. Particularly in the case of acute cerebral infarction is opinion divided, although more agreement has been reached on the value of these drugs in recurrent episodes of cerebral ischemia, especially when these are associated with carotid, vertebral, or basilar stenosis.[1,2] Previous work[3,4] has suggested that a short course of anticoagulants can improve the immediate outlook of cerebral embolism and of some types of nonembolic cerebral infarction. In particular, ingravescent, or "slow-onset," infarction seemed to respond best to this method of treatment; therefore, a study of a series of patients with the clinical diagnosis of this type of cerebral infarction has been made in order to find out whether improvement in the natural course of this lesion can be shown statistically and, if so, whether this improvement is sufficient to outweigh the hazards of treatment.

Definition and Terminology

A difficulty encountered in this field is terminology. Cerebral infarction is the only certain reliable term used in relation to occluding cerebrovascular disease, and, appropriately, it is a pathologic definition. Hemiplegia or other neurologic deficit associated with vascular insufficiency should be easy to define clinically, but some authorities use hemiplegia to mean a complete paralysis while others speak of "dense hemiplegia," "incomplete hemiplegia," "slight hemiplegia," and so on. The word stroke should probably be abandoned altogether by physicians in the same way that "heart attack" and "brainstorm" have been abandoned, because it is used sometimes to describe the onset of cerebral infarction or hemorrhage, sometimes for the whole course of the episode, and sometimes for the neurologic sequelae remaining. Slow-onset stroke therefore is an unacceptable term for the type of case comprising the present series, and either ingravescent infarction or progressive infarction seems better.

Even more confusion arises in the terminology used to describe the cause of cerebral infarction when no obvious source of embolism can be found. Cerebral thrombosis has been the usual descriptive term for this, but it now appears that other conditions are important in producing infarction of the brain.

First, in many patients with cerebral infarction, it has been impossible to demonstrate any clot, either by arteriography[5] or at autopsy,[6] although later work[7] has suggested that some small, proved thrombotic lesions escape arteriographic diagnosis and another later report[8] has shown that at autopsy small clots are often destroyed by the practice of cutting the brain while it is soft. It is therefore probably unjustifiable to say that clotting has not occurred because no clot has been found.

Secondly, considerable attention has been focused on the internal carotid and vertebral arteries in the neck, and many studies have been made on the effects of arterial occlusion in this region, with reviews by Symonds[1] and the classic studies of Hutchinson and Yates.[9] There seems no doubt that arterial occlusion in the neck may produce cerebral infarction without a cerebral clot.

Thirdly, arteriosclerotic disease of the brain has been shown to produce a state of general cerebrovascular insufficiency which may pro-

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ceed to a particular and selective ischemia or infarction by reason of focal arterial narrowing combined with systemic hypotension.[10] In this respect, the experimental work of Meyer and Denny-Brown[11] is of interest because they showed that in monkeys collateral circulation of the brain is at first opened up by lowering of intraluminal pressure but that, when this pressure falls below the critical level of 50 mm. Hg, the whole system collapses and a reversible ischemic anoxia of the brain is converted without thrombosis or embolism to irreversible infarction. In spite of this, the experience of Adams[8] suggests that this is an uncommon cause of major cerebral infarction and one often accepted too easily at post mortem. He suggests that, if the arterial tree from aorta to infarct is carefully examined and search made assiduously for source of embolism, in the vast majority of cases some evidence of thrombotic occlusion of the vessel supplying the infarct will be found.

In view of the above differing etiologies of cerebral infarction, it would be as well to define the terms used here and in general to describe the condition under discussion. The phrase "cerebral thrombosis" is commonly applied to the syndrome of cerebral infarction without embolism and has become such a part of current medical terminology that it will be difficult to discard altogether. However, it should now only be used for those cases where the presence of an intracranial clot can be established. In other cases, either the term atheromatous cerebral infarction or ischemic cerebral infarction may be applied if there is no evidence of any clot or of any embolic source. These terms are also suitable whether the atheromatous or stenotic lesion is intracranial or extracranial. To include all patients, the phrase "cerebral infarction," without qualification, is obviously more correct but has the disadvantage of including patients with cerebral embolism; although the term "cerebral thromboembolism" is used and accepted widely in North America, the possible difference of response to treatment of the two syndromes makes this conjoined term undesirable except as a provisional diagnosis. An alternative is "nonembolic cerebral infarction."[4] This phrase is a little clumsy and not always correct, since it takes no account of symptoms produced by the distal embolism of a cerebral or cervical arterial thrombus. In order to avoid clinical error, it may be necessary to either be content with a description of the neurologic disability or use the pathologic term cerebral infarction to describe a clinical syndrome. Perhaps even the phrase "clinical cerebral infarction" may be accepted for the present.

PATIENTS INVESTIGATED

The series was selected from all patients with acute cerebrovascular lesions who were admitted to the Ashford Hospital, Middlesex, during the years 1956, 1957, 1958, and 1959 (Table 1).

Selection of patients. The selection of patients for the controlled clinical trial was made on previous experience in the treatment of cerebral infarction.[3,4,12,13] It had been found that severe hypertension with a persistent diastolic pressure above 120 mm. Hg, age above 70 years (with few exceptions), bloodstained or xanthochromic cerebrospinal fluid, sudden onset of infarction with a complete lesion and perhaps unconsciousness, hepatic disease, and past peptic ulcer symptoms were all contraindications to anticoagulant therapy. Therefore, the patients selected had a history

TABLE 1
ANALYSIS OF PATIENTS ADMITTED TO ASHFORD HOSPITAL WITH ACUTE CEREBROVASCULAR LESIONS

Year	*Number of patients*	*Male*	*Female*	*Embolism*	*"Thrombosis"*	*Hemorrhage*
1956	140	67	73	9	63	68
1957	147	70	77	10	66	71
1958	147	72	75	8	72	67
1959	136	73	63	7	76	53
Total	570	282	288	34	277	259

of onset within forty-eight hours, progression of symptoms over a period of two hours or more, a diastolic blood pressure of 120 mm. Hg or below, and no macroscopic blood in the spinal fluid. In the four years, 83 patients out of 277 admitted with a diagnosis of "cerebral thrombosis" satisfied the above criteria, but 3 were not included on account of a past history of peptic ulceration and hematemesis, leaving 80 patients for the trial. Alternate patients were treated by anticoagulants in the following way.

Method of treatment. On admission, 12,500 units (125 mg.) of heparin were given intravenously and 200 mg. of phenylindanedione (Dindevan) orally; 2 further similar doses of heparin were given intramuscularly at six-hour intervals. During the second twenty-four hours of treatment, 150 mg. of the oral anticoagulant was administered in divided doses; thereafter, sufficient was given to keep the prothrombin time between 2 and 3 times the normal for three weeks. In the fourth week, the dosage was slowly reduced to prevent sudden increase in the coagulability of the blood. In 1 patient, owing to sensitivity (diarrhea and slight generalized erythematous rash), the phenylindanedione was replaced with biscoumacetate (Tromexan).

Diagnosis. The diagnosis of cerebral infarction is more difficult than is at first apparent because primary cerebral hematoma and tumor can imitate it very accurately.[2,14] However, with the present criteria for selection of patients—slow onset, progressive neurologic deficit, slight or no loss of consciousness, clear cerebrospinal fluid, and absence of gross hypertension—most but not all of the difficulties are overcome. Carotid arteriography would further assist diagnosis but may be unjustified in incomplete lesions where atherosclerosis is certain to be present. Puncture of the carotid artery by a needle may well produce vasoconstriction with distal effects, and it is doubtful whether injection of the dye is likely to improve the circulation. In view of this, arteriography was not performed in this series; in this connection, it is of interest to note that, in proved cases of primary intracerebral hematoma, McKissock, Richardson, and Walsh[15] found that the accuracy of this investigation was only 69%. They also point out that a small percentage of their patients showed slow onset, no loss of consciousness, no hypertension, and clear cerebrospinal fluid, all of these features being more characteristic of infarction.

In the present series, however, in addition to the diagnostic criteria required for the selection of patients, the step-like pattern of progressive neurologic deficit was diagnostically helpful, with either sudden deepening of the degree of weakness or spread of this to previously unaffected areas. In addition, the signs were usually confined to the territory of one of the major cerebral arteries, although even here there is the occasional risk of confusing a middle cerebral type of infarction with a unilateral brain stem lesion.

It appears, therefore, that this series is in no way exact diagnostically since angiography was not performed, and it also must lack something in completeness because some patients with cerebral infarction show xanthochromic or even blood-stained cerebrospinal fluid and these are not included. Since it is agreed that this type of patient is unsuitable for anticoagulants, the point is not important.

Mistakes in diagnosis are inevitable, though not always recognized. In this series, known mistakes were made in 4 out of 80 patients, by chance 2 in the control group and 2 in the treated group; 1 patient in the treated group gave what seemed to be a classic story of cerebral infarction increasing in severity over four days. At autopsy, a clot was present in the right middle cerebral artery and a cavity was found in the infarcted area. This proved to be an astrocytoma. This seemed an example of a cerebral thrombosis spreading back from a tumor. No hemorrhages were found in the brain. The second patient, in the control group, complained of increasing weakness of left arm and leg over a period of twenty-four hours, was normotensive, and had clear cerebrospinal fluid. Her progress was a little unusual because she became confused; arteriography followed by operation showed a primary intracerebral hematoma. The third patient, also in the control group, had a history suggesting basilar occlusion and died suddenly with the signs of subarachnoid hemorrhage. Autopsy showed gross basilar artery stenosis, infarction of the right occipital lobe, and an unsuspected meningioma which had

ruptured the cavernous sinus. The fourth patient had a story suggestive of left cerebral hemisphere infarction, but she grew worse on anticoagulant therapy. At autopsy, a soft infiltrating glioma was present where the infarct was expected and there were recent hemorrhages medially to the tumor, with some blood in the lateral and third ventricles.

Distribution of infarction. The distribution of cerebral infarction was commonly in the middle cerebral territory, and, of the 76 patients finally accepted for the trial, 65 were in this group. Of the others, 8 were in the vertebral-basilar territory with brain stem lesions group; 2 showed posterior cerebral artery occlusion and 1 anterior cerebral. This proportion of 6 middle cerebral to 1 elsewhere is less than the usual 7 to 1 for all types of infarction[12,16,17] but greater than the ratio found by Adams.[8] He investigated 58 patients suffering from cerebral thrombosis over a five-year period and found middle cerebral involvement in 22, vertebral-basilar in 22, posterior cerebral in 4, lateral medullary syndrome in 3, and uncertain in 7. This surely must have been a very selected group.

Analysis of material. The original series of 83 patients had been reduced to 76 owing to known diagnostic mistakes in 4 patients, 2 treated and 2 untreated, and because 3 patients were excluded on account of dyspeptic histories. The final total comprised all patients under 70 years of age with a gradual onset of cerebral infarction who retained consciousness or whose loss of consciousness was minimal. The cerebrospinal fluid was macroscopically normal in all, and diastolic blood pressures were not above 120 mm. Hg. The treated and untreated groups each included 38 patients. These are analyzed according to age and sex in Table 2, where it can be seen that the distribution is reasonably even between the 2 groups and that over half the patients are in the age group 60 to 69. The preponderance of men to women is 4 to 3; this is in agreement with other authorities for these age groups,[17–19] although it has been shown[4,16] that women outnumber men in the over-70 age group suffering from cerebral infarction.

TABLE 2
ANALYSIS OF SERIES ACCORDING TO AGE AND SEX

Age	*Number of patients*	*Treated*		*Untreated*	
		male	*female*	*male*	*female*
40-49	8	2	2	3	1
50-59	26	7	5	8	6
60-69	42	12	10	12	8
Total	76	21	17	23	15

RESULTS

Assessment. The patients were followed up for six months and then an assessment was made by clinical examination. They were divided into 4 groups: recovered, improved, not improved, and died.

Recovered. This meant that the patient noticed slight or no disability and was able to resume normal life without help and return to full work. Some loss of fine-movement dexterity in the hand was considered compatible with full "recovery" if the above criteria were fulfilled. Probably, all patients with initial complete hemiplegia continue to show slight pyramidal signs permanently.

Improved. This meant some useful movement was possible at the elbow and wrist and that the patient required only slight assistance to get about and live a useful life. Some work was possible, and walking with a stick was reasonably well tolerated.

Not improved. This implied no return of arm movement below the shoulder and a poor recovery in the leg, so that considerable assistance was needed for the patient to get about. Return to work was not possible. This group included the bedridden patients.

Analysis. The results are analyzed in Tables 3 through 7. It can be seen that, in the untreated series, half the patients are recovered or substantially improved at the end of six months. This confirms former work on the natural history of nonembolic cerebral infarction,[4,16] although my figures for the years 1952 to 1955 were a little better than those for 1955 to 1959. Table 3 shows that prognosis worsens with age, since, in the age group 40 to 49, 3 patients out of 4 showed a good result; in the group 50 to 59, 8 out of 14; and in the group 60 to 69, 19 out of 38, although the groups are not numerically comparable. The improvement with treatment was more marked in the 50 to 59 group than in the older patients, but the death rate was

TABLE 3
RESULTS IN UNTREATED SERIES

Age	Number of patients	Recovered	Improved	Not improved	Died
40-49	4	2	1	1	0
50-59	14	5	3	4	2
60-69	20	4	4	7	5
Total	38	11	8	12	7

TABLE 4
RESULTS IN TREATED SERIES

Age	Number of patients	Recovered	Improved	Not improved	Died
40-49	4	2	2	0	0
50-59	12	5	4	2	1
60-69	22	6	7	7	2
Total	38	13	13	9	3

TABLE 5
RESULTS IN UNTREATED INCOMPLETE LESIONS

Age	Number of patients	Recovered	Improved	Not improved	Died
40-49	2	1	1	0	0
50-59	7	2	2	2	1
60-69	11	2	2	4	3
Total	20	5	5	6	4

TABLE 6
RESULTS IN TREATED INCOMPLETE LESIONS

Age	Number of patients	Recovered	Improved	Not improved	Died
40-49	2	2	0	0	0
50-59	7	2	4	1	0
60-69	13	4	5	3	1
Total	22	8	9	4	1

TABLE 7
RESULTS IN TREATED AND UNTREATED PATIENTS

		Anticoagulant treatment				No anticoagulant treatment			
		Lesion incomplete		Lesion complete		Lesion incomplete		Lesion complete	
Year	Number of patients	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died
1956	22	5	2	3	1	4	3	1	3
1957	18	5	1	2	1	2	2	2	3
1958	20	4	1	3	2	2	4	3	1
1959	16	3	1	1	3	2	1	3	2
Total	76	17	5	9	7	10	10	9	9

lowered in equal proportions in both these groups.

The over-all effect of anticoagulant treatment in this series of slow-onset infarction can be seen by comparing Tables 3 and 4. The recovery rate was raised from 50 to 70%, and, although this was not quite statistically significant ($P = 0.09$), it was sufficiently encouraging to suggest that the treatment might be of value if the selection of patients could be even more stringent. It was decided to study first the influence of the rate of development of the infarction on the prognosis of untreated patients. The time of development varied in this series from two hours to two weeks, about half the patients falling in the nineteen-to-twenty-four-hour group. No relationship could be established, so it was concluded that, apart from sudden infarction, the rate of evolution of the neurologic lesion is not important in untreated patients.

The value of treatment in relationship to speed of development of lesion seemed at first easy to study, but it was soon realized that effective treatment of a patient whose condition is worsening may well preclude the observer from judging the length of time the lesion would have taken to evolve if untreated. This particular investigation was therefore abandoned, so that at least a definition of

degrees of slowness of a slow-onset infarction became unnecesary.

The other obvious attribute of the lesion which could be studied was its severity. In the untreated group, lesions which were incomplete on admission surprisingly had no better prognosis than those which were complete. In the treated group, however, the recovery rate was raised from 56 to 80%. This is not only encouraging but statistically significant ($P < 0.05$) and confirms previous work,[12] suggesting that the best results of anticoagulant treatment will occur in patients whose lesions are slowly getting worse. This suggests that progressive infarction may be a more acceptable term than ingravescent infarction.

PATHOLOGIC MATERIAL

There were 7 deaths in the untreated series, 5 in the age group 60 to 69, and 3 deaths in the treated series, with 2 of these over 60. Only 8 autopsies were obtained because 2 of the untreated patients died at home. These 2 deaths were sudden, occurred in bedridden patients, and, on the clinical evidence, might well have been due to pulmonary infarction. Among the 5 untreated patients, pulmonary infarction was the cause of death in 3, diffuse bronchopneumonia in 1, and complete basilar occlusion in 1. Of the 3 patients dying of pulmonary infarction, 1 had a complete carotid occlusion and the other 2 midcerebral thrombi. Of the 3 treated patients coming to autopsy, 1 had a massive infarction of the brain with no obvious thrombus but with gross atheroma of the cerebral vessels, 1 had a small occluding thrombus in the midcerebral artery with a rather hemorrhagic infarction beyond, and the third showed carotid stenosis and an unsuspected carcinoma of the bronchus.

These findings, although few in number, confirm previous experience[12] that anticoagulants reduce the death rate in cerebral infarction by protecting the patient from pulmonary infarction; this protection in patients over the age of 50 is in agreement with recent experience in traumatic surgery.[20]

DISCUSSION

This series suffers from the disadvantages of selected and incompletely investigated material, and therefore any conclusions are open to criticism. Selected material is always suspect because the selection is made by the observer himself, whose previous work may have suggested the likely lines which show promise. If, however, the standards for selection are definite and capable of objective measurement, selection is at least consistent. In this series, age was thought to be accurate in assessment and was confirmed by relatives. The diastolic blood pressure is said to be unreliable, and any figure for selection is arbitrary. Nevertheless, previous experience had shown that more bleeding troubles arose when the diastolic pressure was persistently above 120 mm. Hg, and repeated observations made by the same person were found to be necessary. The cerebrospinal fluid was examined macroscopically only, and the presence of blood or yellow pigment was a simple and reliable observation. Attention has already been drawn to the fact that some cerebral infarcts produce yellow or blood-stained cerebrospinal fluid, and patients with such spinal fluid are therefore not included in this series.

Possible criticism of incomplete investigation is more difficult to answer and is valid. Arteriography, the investigation likely to make the diagnosis complete, has been discussed already. Recently, Bull, Marshall, and Shaw[21] have shown that arteriography was of value in only half their patients with recent acute cerebrovascular lesions and that complications occurred in 9% of their patients. It seems, therefore, that ethical considerations preclude using this method routinely at present in atheromatous patients whose lesions are recent but incomplete.

Mechanism of treatment. The mechanism of anticoagulant treatment once cerebral infarction has taken place is not completely understood, but the beneficial effect can occur in one or more of three ways. First, anticoagulants may prevent clot formation in patients whose infarctions were originally due to atheromatous narrowing combined with sufficient systemic hypotension to produce anoxia or ischemia. The studies of Denny-Brown and Meyer[22] are interesting in this connection. These workers studied the effects of ischemia on the cerebral cortical vessels of monkeys. They showed that, as a result of ischemic anoxia, stasis occurs on the venous side of the

capillary cortical network with segmentation of red cell masses. Providing this stasis had not been present more than fifteen minutes, it could be reversed by raising the systemic blood pressure. The administration of heparin appeared to make the production of further stasis more difficult for from three to four hours but did not reverse this stasis unless there was an associated rise of blood pressure. Second, anticoagulants may prevent the spread or propagation of clot from the original thrombus. This spread may occur distally or centrally and, by involving anastomotic vessels, may cause increase in the extent of the infarction. Third, anticoagulants may prevent distal embolism from large thrombosed vessels such as the carotid or vertebral arteries into small peripheral vessels, many of which have little evidence of collateral circulation. It is in this prevention of embolization and of recurrent thrombus that anticoagulants have achieved their major therapeutic successes outside neurology, and it may be that most help from anticoagulants will come in this way to neurologic patients. However, it is well to remember that apparently adequate prolongation of the prothrombin time will not always prevent thrombosis from occurring, and many physicians will have known the disappointment of a major thrombus striking at this time.

Dangers of treatment. The evident dangers of anticoagulant treatment, which have been rightly emphasized by most authors, are three in number. The first is bleeding into and around the infarcted brain; the second is major visceral bleeding producing hypotension; and the third is the risk of treating intracranial hematomas with anticoagulants because of errors in diagnosis.

Medical opinion is sharply divided on the possibility and extent of bleeding around or into infarcted brain. Experimental work suggests that anticoagulants do considerable harm in this way.

Sibley, Morledge, and Lapham[23] showed that experimental hemorrhagic cerebral infarcts in dogs would bleed further after the administration of Dicumarol, but when the infarcts were anemic no such tendency was found. Moyes and associates[24] showed that infarctions produced in dogs by injecting plastic vinyl acetate into the internal carotid artery were more hemorrhagic in animals having anticoagulants. Similarly, Peterman and associates[25] produced cerebral infarction in dogs by the intracarotid injection of blood clot. After three days, about half the animals were given Dicumarol, and, at the end of fifteen days, the infarctions in the treated animals were conspicuously more hemorrhagic and the mortality was higher.

Clinically, however, the evidence against anticoagulants is less strong. Fisher[18] found no evidence that anticoagulants cause hemorrhage into infarcted brain, and my experience[3,4] agrees with this.

Similarly, Wright and McDevitt[26] found no clinical evidence that anticoagulant treatment was harmful, even in hemorrhagic cerebral infarction. Brain[27] thinks it unwise to give anticoagulants within at least three weeks of an attack of cerebral infarction, and this view is suported on the Continent by de Morsier and Tissot.[28] Vastola and Frugh[29] have reported a very disturbing series of 55 consecutive patients with recent cerebral infarction treated by anticoagulants. There was no control series, but the authors did not think their patients showed improvement as compared with that "expected in a similar group;" 20 of the 55 patients bled in various parts of the body, and, in 4, anticoagulants were blamed for extensive brain hemorrhage—3 into the infarct and 1 elsewhere. On the other hand, Wells[30] treated with anticoagulants 29 patients with 34 attacks of cerebral embolism, with results better than in his untreated series and without intracranial bleeding.

The second danger of treatment—that of visceral bleeding—seemed at first a major risk, particularly in the elderly. In the second half of this series, when the dosage of anticoagulants was reduced, 17 minor hemorrhagic episodes arose in 9 patients. Of these, hematuria accounted for 7, epistaxis for 5, subconjunctival hemorrhage for 3, and facial bleeding after shaving for the other 2, In only 1 patient was the prothrombin time found to be over 40 sec., and in all the patients treatment was resumed after a two-day interval. Luckily, no major visceral bleeding was encountered in the last three years, and no patient had to be withdrawn from the treated group. Some per-

sons may bleed severely, of course, even if the prothrombin time is not unduly raised, and the patient's condition is a more important guide than the results of blood estimations. Thus, the continued use of anticoagulants is always dangerous if any visceral or serious superficial bleeding arises, even though the prothrombin time is reasonably low.

The third danger is mistaken diagnosis. The differentiation between cerebral infarction and intracranial hematomas has already been discussed. Fortunately, the type of infarction that can suitably be treated by anticoagulants is not the most likely to be mistaken for hemorrhage, although a small but disturbing proportion of intracerebral hematomas have a slow onset without loss of consciousness, without hypertension, and with clear cerebrospinal fluid,[15] all of which are usually characteristic of infarction. But, in addition, the stepwise course of ingravescent infarction and its adherence to the distribution of a major cerebral artery are of assistance in avoiding obvious error.

CONCLUSIONS

The results of anticoagulant treatment in a selected series of patients with the clinical diagnosis of cerebral infarction suggest that the progressive type of infarction in a normotensive patient responds best to this form of therapy. The reduction in death rate in the treated patients was due almost entirely to the prevention of pulmonary infarction, so that anticoagulants have not changed the survival rate associated with the effects of the cerebral infarct alone. They have, however, improved the prognosis for recovery of function and, if used for suitable patients, do not seem to carry very much risk.

SUMMARY

A series of 76 patients was selected from 277 patients admitted to Ashford Hospital, Middlesex, during 1956, 1957, 1958, and 1959 with the clinical diagnosis of cerebral infarction.

The selection was made by including only those patients below the age of 70 who had a diastolic blood pressure persistently below 120 mm. Hg, macroscopically clear cerebrospinal fluid, a history of gradual onset of symptoms, and some degree of consciousness preserved. Alternate patients in this selected series were treated with anticoagulant therapy for four weeks, and the results were assessed and analyzed after six months.

Improvement in the treated group occurred, but the results were not quite significant unless further selection was made to include only patients whose lesions were incomplete.

Terminology has been discussed, and the best description of this type of case seems to be progressive cerebral infarction.

It appears that anticoagulant therapy in this series markedly improved the immediate survival rate of cerebral infarction by preventing pulmonary infarction and also improved the recovery rate of patients with progressive cerebral infarction.

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Correction. Unfortunately, Dr. Robert Baker's title was listed incorrectly in the Conference on Vascular Disease of the Brain, which was published in the April issue of NEUROLOGY, Part 2. Dr. Baker's listing should have read: "Assistant Professor of Medicine (Neurology), School of Medicine, University of California at Los Angeles."

A new method for graphic study of human movements

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THE NEUROSURGICAL APPROACH to the correction of disturbances of motility imposes a need for objective analysis of these abnormal movements in order to evaluate the changes brought about in them by placement of therapeutic lesions in the nervous system. From the physiologic point of view, a study of less dramatic but functionally important postoperative changes in the characteristics of movement, such as speed variations, regularity, and response to volition, may prove to have value for an understanding of the effects of intervention on the brain and on the physiologic mechanisms involved. Such an understanding must include a study of all the above characteristics of movement both before and after surgery and must be as free as possible from subjective observation.

In the literature are reported many attempts to obtain objective records from which an analysis of the varied spatial and temporal characteristics of movement could be made. These include direct recording of the movement itself by kymographic, photographic, or cinematographic means and studies by indirect methods such as electromyography.

The problem of analyzing a movement is complicated by three factors. First, movement occurs in space; second, it occurs in a time period during which the successive positions change very rapidly; and third, movement results from the changing position of many parts of the body at the same time. These problems have been only partially solved by the authors who have reported procedures that they employed.

METHODS REPORTED IN LITERATURE

The more or less complicated and perfected technics for electromyographic recording[1,2] are limited by the very specialized information they yield, namely electrical activity.

An actual picture of the course of movement was recorded on a photographic plate by Bernstein,[3] Beall,[4] and others. The attachment of technical equipment to the patient which may have interfered with his natural motion and their limited visualization of the time factor reduced the value of their method, especially when complex or slow movements were under observation.

Evaluation of movement by study of slow motion pictures[5] represents only an improvement over direct visual observation with the same subjective limitations.

Herz,[6] Basler,[7] and Whittier[8] developed methods for semigraphic plus graphic evaluation of motion pictures in order to obtain a better representation of time and space elements. These last authors developed a method of graphic representation from motion pictures by measuring the variation of the joint angle or by locating the moving limb in relation to only one fixed point. They related the movement in space to the temporal factor which

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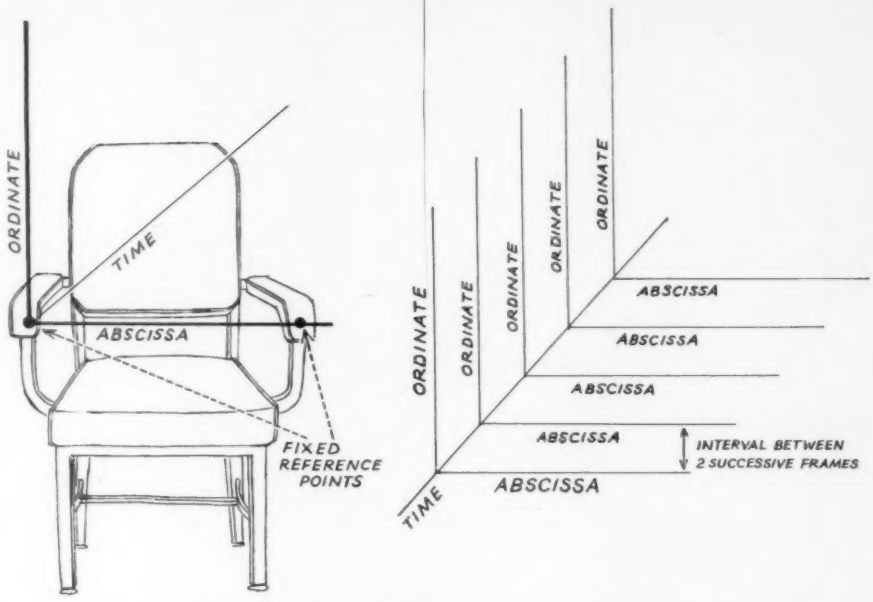

Fig. 1. Orientation of coordinate system based on 2 fixed points

they obtained from the speed of the camera and projected their results on a biaxial coordinate system. Measurements of the joint angle carry the limitations of indirect representation and do not permit the study of complex motions. The variation of distance between two points is not always proportionate to the motion of one of them, and this reduces the accuracy of the second method.

We have based our method on the same idea—that of using the many positions of a movement separately seen in each successive frame of a motion picture and of relating them to the constant time interval between frames.

The position of a point in 2-dimensional space can only be established accurately by 2 spatial measurements. Accordingly, we fixed each position of the entire movement with its coordinates to a biaxial system. These 2 spatial dimensions were related to time as a third dimension.

This investigation was carried out on a series of patients with intention tremor and Parkinson's disease operated upon by Dr. Irving S. Cooper who employed chemothalamectomy.

METHOD

A cinematographic record of the movements under study was made on 16-mm. film exposed at 24 frames per second; 2 fixed points were established in such a place that they were visualized together with the patient on each frame, enabling us to orient our coordinate system in a constant way (Fig. 1). Placement of such points depended on the character of

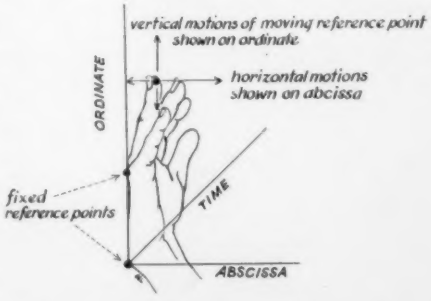

Fig. 2. Orientation of axis of coordinates for study of segmental movements of fingers

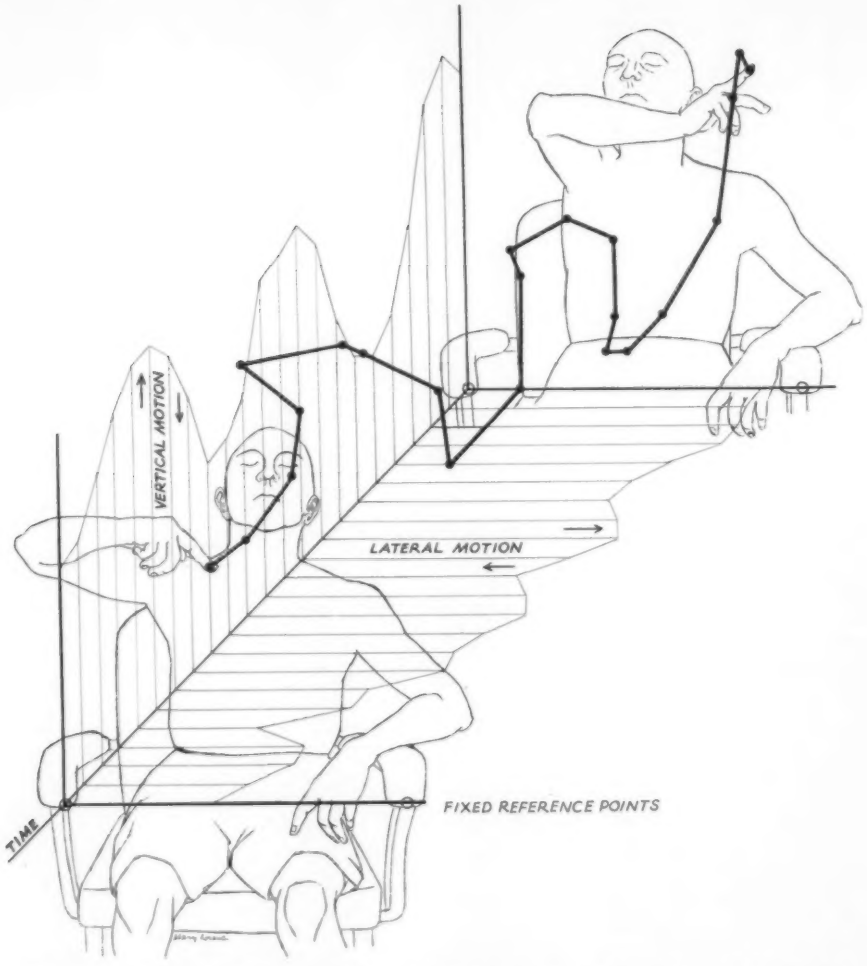

Fig. 3. [A, above] Graphic representation of intention tremor. [B, opposite page] Same task performed after chemothalamotomy

the movement to be studied. Movement involving changes of position of the body as a whole, such as gait, required fixing reference points somewhere within an area around the patient, for example, on a chair or the wall. Study of segmental movement demanded that the 2 points be fixed on the segment closest to that moving portion in which we were interested (Fig. 2). We were now able to measure the 2 coordinates of each successive position adopted by the moving limb in relation to our 2 axes. Next, we related both of these values with the time element (which was established by the interval between successive frames) in a triaxial coordinate system (Fig. 3).

DISCUSSION

There is a serious obstacle to a graphic representation of movement based on a motion picture record. The nature of the reference material and the technical equipment we use can give us only a 2-dimensional projection of a movement which is, in reality, 3-dimensional; 2 dimensions can be recorded simultaneously, but the third—motion toward and away from the recording camera—is always lost. We can resolve this problem in 2 ways. We focus our camera on the plane in which the greatest range of motion occurs, so that the components of movement toward the camera will be minimal and their influence negligible in our graphic system. If we are really to face the

problem of resolution of the third dimension, it is necessary to employ a mirror, placed in such relation to the patient that 2 dimensions are photographed by direct focus and the third recorded simultaneously by its reflection. The mathematical and practical difficulties involved in the last method convinced us that our first solution, that of selective focus, was the more useful.

Movement is basically a transportation of parts of a body or of the whole body in 3 spatial dimensions within a given time. During this time, the moving subject will adopt a number of different positions, which will result in a movement through space. Once we were reconciled to the loss of 1 spatial dimension, we proceeded by establishing reference points for all of the many positions constituting a complete movement on the successive frames of a motion picture (Fig. 4). The time factor

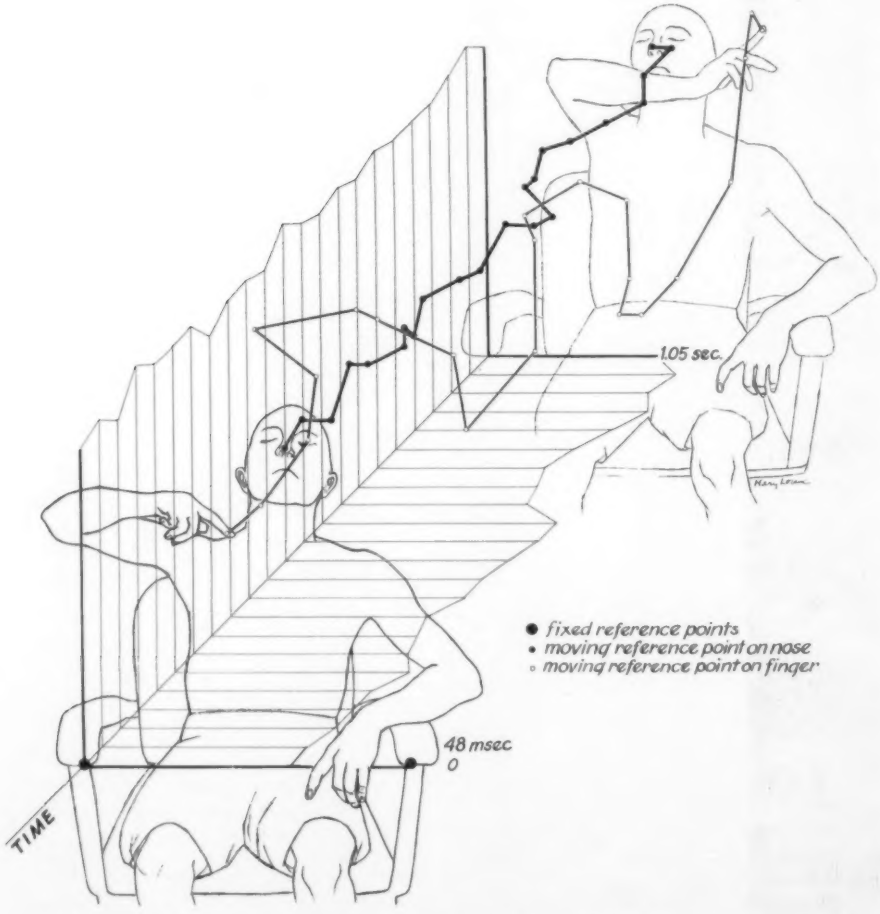

Fig. 4. Relation of tremor of head to intention tremor of arm produced while patient was trying to touch his nose. (Isolated representation of intention tremor of arm can be seen in Figure 3.)

Fig. 5. Succession of frames of a choreiform movement which is shown graphically in Figure 6

was established by the interval between exposures (Figs. 5, 6, and 7).

We have already described our reasoning for the establishment of different reference points depending on the kind of movement being investigated. Thus, our coordinate system is always based on 2 constant points whether they are fixed in the space surrounding a patient's body or on a part of the body itself. Complex movements would require that we actually use several different coordinate systems simultaneously.

Since the usual graph employing a 2-coordinate system is not satisfactory because 2 coordinates are needed for plotting each of the 2 spatial dimensions of a moving point, we needed a system using 3 axes, 2 for spatial components of motion and the other for the time element. This is the system we used, delegating the space components to the X and Y axes and the time component to the Z axis. Our graph assumed the form of a dihedron with its axis representing time (Z) and its vertical and horizontal planes recording the range of motion in lateral and vertical directions. Within the space encompassed by the dihedron, we plotted the curve resulting from the 3 elements we used in our study. An example is seen in Figure 8. Such a graph is simply a "stretching" within time of the actual course of the movement. The study of such a graph provides us with not only accurate qualitative characteristics of a movement such as direction and rhythm but also the quantitative character such as its total speed and its acceleration or deceleration (Fig. 9). The quantitative values obtained from these graphs can add valuable information to our knowledge of the organization of a movement.

In Figure 10, we show a pre- and postoperative graphic analysis of speed variations of an intentional movement in a patient who suffered from familial intention tremor. Notice how the speed variation at each moment of the movements became regularized after the operation. In the preoperative graph, the tremor is shown by sudden and rapid increases of speed followed by a period of deceleration.

SUMMARY

A method of graphic registration of movements from motion picture records is pre-

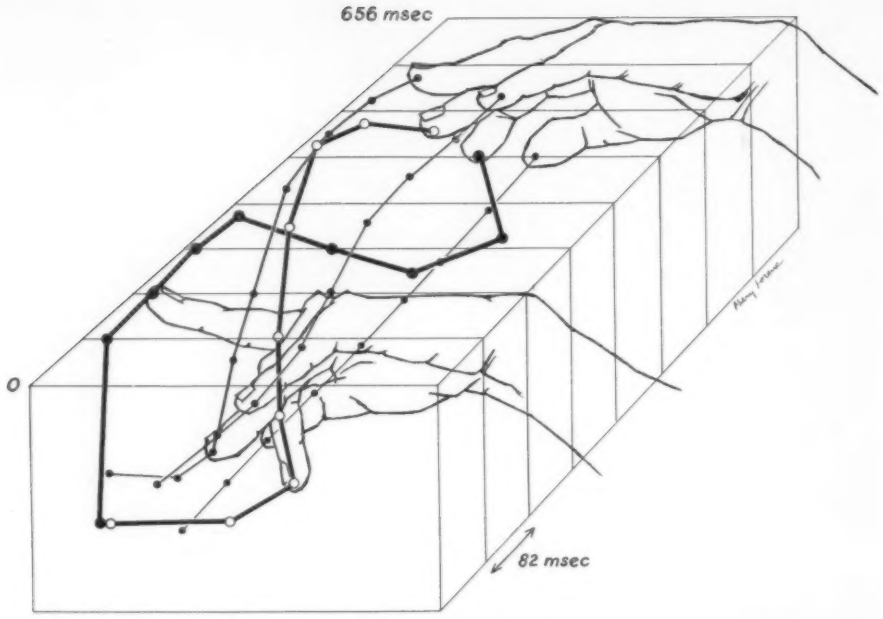

Fig. 6. Complex choreiform movement of hand involving mostly the fingers. This movement is further analyzed in Figure 7.

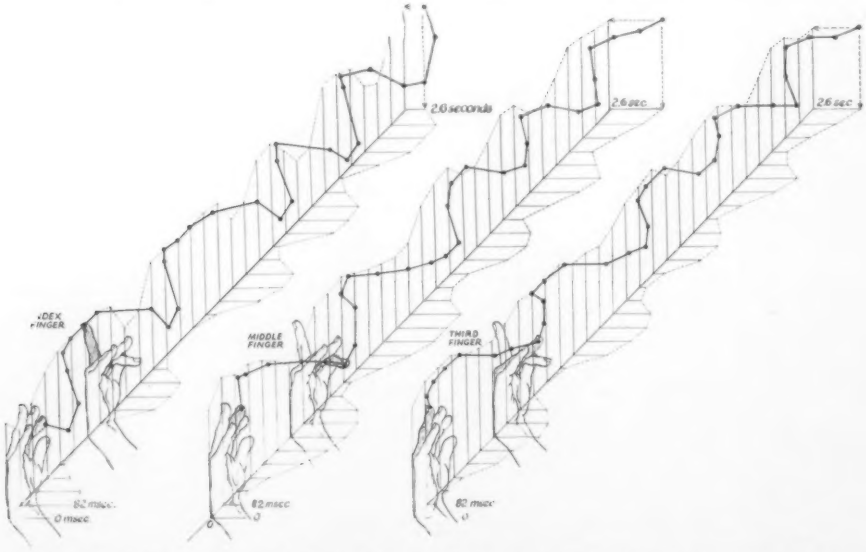

Fig. 7. Analysis of motion of individual fingers which constitute choreiform movement as shown by Figures 5 and 6. Notice pattern of apparently anarchic movement.

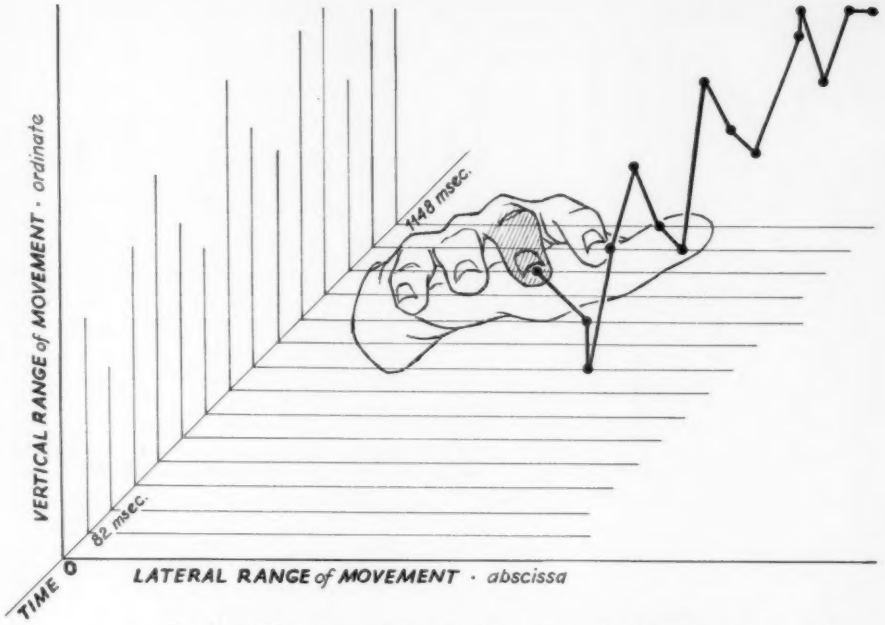

Fig. 8. Graphic representation of resting tremor of parkinsonism

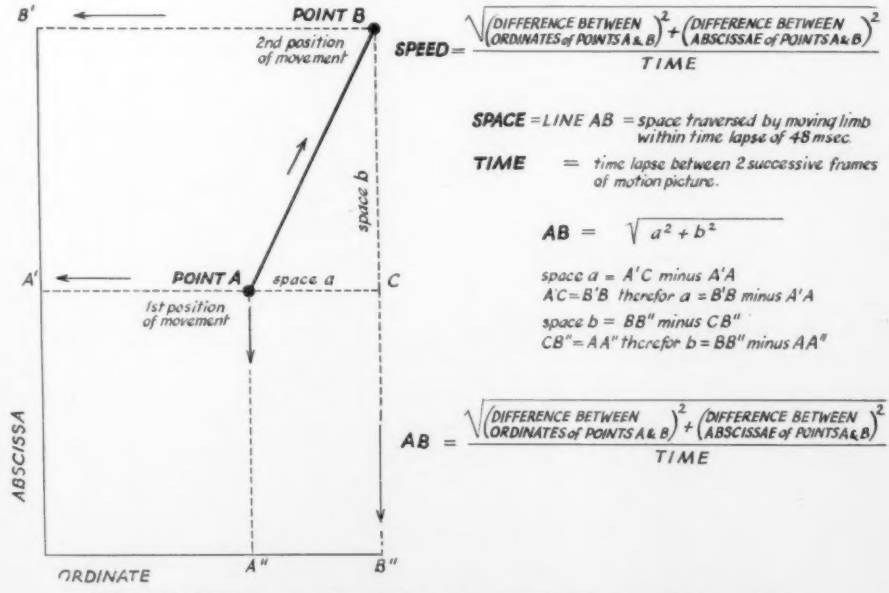
B'
POINT B
2nd position of movement
space b
A'
POINT A
space a
C
1st position of movement
ABSCISSA
ORDINATE
A"
B"
SPEED = √((DIFFERENCE BETWEEN ORDINATES of POINTS A & B)² + (DIFFERENCE BETWEEN ABSCISSAE of POINTS A & B)²) / TIME
SPACE = LINE AB = space traversed by moving limb within time lapse of 48 msec.
TIME = time lapse between 2 successive frames of motion picture.
AB = √(a² + b²)
space a = A'C minus A'A
A'C = B'B therefor a = B'B minus A'A
space b = BB" minus CB"
CB" = AA" therefor b = BB" minus AA"
AB = √((DIFFERENCE BETWEEN ORDINATES of POINTS A & B)² + (DIFFERENCE BETWEEN ABSCISSAE of POINTS A & B)²) / TIME

Fig. 9. Explanation of method of determining speed of movement from our graphs

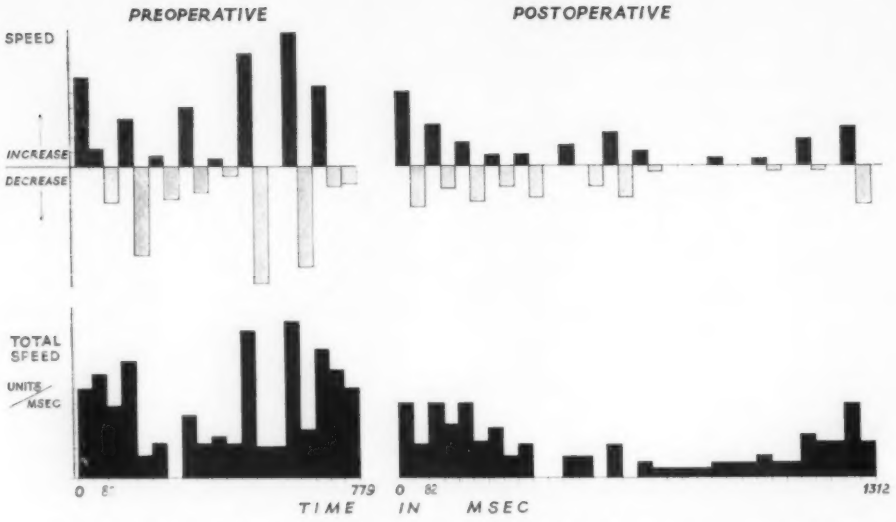

Fig. 10. Graph showing speed variations during performance of an intentional movement (finger to nose). Upper graph represents variations of speed during each time interval; lower graph represents total speed of same movement. First part of both graphs shows a complete finger-to-nose movement before operation. Second part shows same movement after chemothalamectomy.

sented. Accurate geometric fixation of every successive position constituting a movement permits more complete analysis of its quantitative and qualitative characteristics. Some examples of such analyses are presented.

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Acute inclusion encephalitis of herpes simplex type

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J. Claude Gaulin, M.D.

ENCEPHALITIS caused by the virus of herpes simplex is a rare condition. According to Haymaker,[1] Ginder and Whorton,[2] and Smadel and Adair,[3] the essential criteria for this diagnosis are the presence of intranuclear, eosinophilic inclusions in neurons and glia and isolation of the virus from brain tissue. Smith, Lennette, and Reames[4] were the first to report a case diagnosed by these criteria. Since then, at least 10 additional cases have been reported.[2,5–9] In all of these cases, the diagnosis was made post mortem. There have also been many case reports, which will be referred to later, wherein a diagnosis of herpes simplex encephalitis was suspected by clinical and pathologic evidence but not proved.

In addition to the cases which have been studied pathologically, there have been some reports of nonfatal meningitis or meningoencephalitis allegedly caused by the virus of herpes simplex. Smadel and Adair[3] stated that, in such cases, the criteria for proof that a given episode is due to the herpes simplex virus are: (1) demonstration of the absence of specific antibodies in the acute-phase serum and the appearance of these antibodies in the convalescent serum and (2) isolation of the virus from the cerebrospinal fluid. Armstrong[10] reported a case diagnosed clinically as lymphocytic choriomeningitis, but no antibodies against the virus of this disease were found in the serum. Herpes simplex virus was isolated from the cerebrospinal fluid and specific herpes neutralizing antibodies developed in the patient's serum following recovery. The patient of Fisher and Patrick,[11] with a clinical diagnosis of polioencephalitis, was discharged improved two months after admission to hospital. In this case, although herpes simplex virus was isolated from the cerebrospinal fluid and although a relatively high level of neutralizing antibodies was present in the serum at that time, the authors concluded that the lack of rise in titer precluded a diagnosis of disease due to herpes simplex virus. Afzelius-Alm[12] collected 11 cases which he termed encephalomeningitis and in which he demonstrated a rise in herpes simplex antibody titer by complement-fixation or neutralization test or both. The virus of herpes simplex was isolated from the cerebrospinal fluid in 1 case. However, 2 of these cases are doubtful, for, in 1 (Case 4), no lumbar puncture was performed and, in another (Case 6), there were no cells in the cerebrospinal fluid. All of these patients either improved or recovered.

The purpose of this communication is to present a case of encephalitis with an acute onset in which eosinophilic, intranuclear inclusions were found by brain biopsy and in which there was a fall in the herpes simplex complement-fixing antibody titer on the forty-fourth day of the illness. This patient has been the subject of two previous articles written while he was still alive. One author, Kurtzke,[13] regarded this case as an instance of Dawson's encephalitis; the other authors, Dodge and Cure,[14] thought that the probable etiologic

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agent was the virus of herpes simplex. Moreover, Haymaker and associates[9] included this patient in their 37 cases of acute encephalitis with nuclear inclusions in adolescents and adults. The latter considered the diagnosis of herpes simplex encephalitis to be equivocal on the basis of the serologic findings and the failure to isolate the virus from brain tissue. We now have the opportunity of reporting this case completely, including the findings of postmortem examination.

CASE REPORT

This 20-year-old white male in whom headache, nausea, and vomiting developed on June 22, 1953, was kept over night in an emergency ward of the United States Army Hospital, Fort Campbell, Kentucky. During the night, he was uncooperative, incoherent, and exhibited bizarre behavior. He was admitted to the hospital on the following day.

Physical examination. Temperature was 102.4° F. rectally, pulse was 100, respirations were 25, and blood pressure was 148/74. The general physical examination was normal; no skin lesions were noted. The neurologic examination revealed that the patient was disoriented, agitated, and uncooperative. The fundi were normal. The remainder of the neurologic examination was normal.

Laboratory data. Urinalysis, hemoglobin, and erythrocyte count were normal. Leukocyte count was 11,650 per cubic millimeter with normal differential. Blood glucose and urea nitrogen were normal. A lumbar puncture on June 23 revealed 488 white cells per cubic millimeter, of which 33% were polymorphonuclears and 67% were lymphocytes.

The patient was treated with intravenous dextrose in saline and an antipyretic.

On June 24, the temperature ranged from 103.6 to 104.8° F.; pulse, 80 to 108; and respirations, 22 to 34. He was comatose and exhibited nuchal rigidity. A second lumbar puncture yielded a clear, nonbloody fluid under a pressure of 350 mm. of fluid containing 457 white cells per cubic millimeter with 48% polymorphonuclears and 52% lymphocytes; total protein, 144 mg. per cent; sugar, 69 mg. per cent; chlorides, 722 mg. per cent; and colloidal gold curve, 1112332100. The complement-fixation test for syphilis was negative. A smear revealed no bacteria and a culture showed no growth of organisms. Treatment consisted of oxygen, intravenous fluids, penicillin, streptomycin, adrenal cortical extract, vitamin C, and cold packs.

On June 25, the temperature was still elevated to 104° F. Neurologic examination revealed nuchal rigidity and stupor. The patient could be aroused to grasp with the right hand but not with the left. There was no papilledema, and the pupils reacted to light. The right patellar reflex was absent, the left active; the plantar response on the left was extensor. A roentgenogram of the chest revealed a generalized increase in bronchovascular markings with a rather peculiar peribronchial infiltrate, suggesting either aspiration of material or cardiac decompensation. Roentgenograms of the skull revealed displacement of the calcified pineal gland posteriorly and to the left of the midline. A ventriculogram showed displacement of the third ventricle 14 mm. to the left of the midline and elevation of the right temporal horn and a portion of the right occipital horn.

On June 25, a right temporoparieto-occipital craniotomy was performed. The dura was extremely tightened; when it was incised, the brain tissue herniated. There were tiny punctate hemorrhagic areas on the surface of the cortex. The brain appeared markedly softened. Exploration revealed no evidence of tumor. Although an attempt was made to resect portions of the temporal and occipital lobes, this was made difficult by the severe cerebral edema, and the attempt was abandoned. Needle biopsy was performed, and pieces of temporal and occipital lobes were removed for histologic examination. The bone flap was discarded and the galea and skin were closed.

On June 26, the temperature was elevated to 105° F. He responded only to pinprick by developing a bilateral decerebrate posture; on the following day, this posture was observed only on the left side. The pupils were equal and reacted to light. Because of the development of dyspnea and retained secretions, a tracheotomy was performed on June 27 with subsequent improvement in respirations. Mild, fine tremors of the lower extremities and the lower jaw were observed on June 28; the administration of 0.1 gm. of Dilantin three times a day was started. Penicillin and streptomycin were continued.

By June 29, the temperature was only 101° F. However, because of the development of a fixed, dilated left pupil; a rise in blood pressure; an unstable pulse; and a tight, nonpulsating scalp flap, it was decided to reopen the previous operative site. This was done on June 29. A considerable amount of degenerated, soft brain tissue was extruded, which was suctioned from the wound. The scalp flap was opened further until the whole area was exposed. There were multiple areas throughout the temporal, parietal, and occipital lobes that were hemorrhagic and other areas in which, on suctioning, small "nodules" of firmer brain tissue were found. As the brain continued to herniate, it was removed until finally the temporal horn of the right lateral ventricle was entered. Inspection of its interior failed to reveal any pathology. More of the right temporal and occipital lobes and a small portion of the parietal lobe were removed. Finally, the flap was reflected back and the galea and skin approximated. During this operation, many specimens of brain tissue were removed for histologic examination.

Postoperatively, the patient was stuporous, moved

the right extremities, and exhibited a left-sided decerebrate posture. During the next few days, his temperature ranged from 100 to 103° F., tracheobronchial secretions were profuse, and he had a few seizures. He would occasionally grasp weakly with his right hand on command.

On July 14, a meningitis caused by Neisseria intracellularis developed, which responded satisfactorily to antibiotics. A lumbar puncture on August 22 revealed a clear, colorless fluid under a pressure of 85 mm. containing 75 lymphocytes per cubic millimeter; total protein, 66.2 mg. per cent; sugar, 42 mg. per cent; and culture, no growth.

His condition gradually deteriorated and, by October, he was not responding to painful stimuli. From this time until transfer to the Bronx Veterans Administration Hospital, there was no marked change in his status.

The remainder of the laboratory findings during the patient's stay in the Fort Campbell Army Hospital are now summarized. An electroencephalogram on September 30 revealed a diffusely abnormal record with slow, low voltage activity. Serologic tests yielded negative results for the following diseases: typhoid, paratyphoid, brucellosis, tularemia, infectious mononucleosis, lymphocytic choriomeningitis, Eastern and Western equine encephalitis, mumps meningoencephalitis, and leptospirosis. In an attempt to isolate a viral agent, the brains of adult and suckling mice were inoculated with cerebrospinal fluid obtained on July 27, 1953, but these procedures were negative. According to Dodge and Cure,[14] on November 4, 1953, the one hundred and thirty-sixth day of the disease, cerebrospinal fluid from the lumbar sac and a biopsy of brain adjacent to that removed at the operation were injected into infant and adult mice and embryonated eggs at the Department of Virus and Rickettsial Diseases, Army Medical Service Graduate School, Washington, D. C. No virus was isolated by these methods.

Serologic studies for herpes simplex revealed that the complement-fixation test was positive in a dilution of 1:64 on the fifteenth day of the illness and positive in a dilution of 1:16 on the forty-fourth day of the illness; the herpes simplex neutralization test was positive on the fifteenth and sixty-fifth days of the illness. The table showing these studies for herpes simplex is reproduced here from the paper by Dodge and Cure.[14]

The patient was transferred to the Bronx Veterans Administration Hospital on November 28, 1953. On admission, the temperature was 99.6° F.; pulse rate, 96; respirations, 22; and blood pressure, 130/90. The patient was emaciated, and there were many decubitus ulcers overlying pressure points. There was a sunken 10- by 15-cm. cranial defect in the right parietal region. The patient did not respond to commands and uttered no sounds. In response to threatening gestures, he blinked both eyes; withdrawal of limbs followed pressure applied on the right side but not on the left. The left fundus revealed blurring of the disk margins and a pallor of the disk. The right pupil measured 3 mm. and the left 6 mm. in diameter; they both reacted to light. The patient was continually grinding his teeth, and the jaw could not be opened. Marked rigidity of the neck and trunk was observed. There was marked resistance to passive movements of all 4 extremities, which were held in a flexed posture except that there was extension at the metacarpophalangeal joints with flexion at the distal or interphalangeal joints. All of the deep tendon reflexes were absent, and there were bilateral extensor plantar reflexes. He was incontinent of urine and feces.

A lumbar puncture on December 3, 1953, yielded an opalescent fluid under a pressure of 100 mm. containing 6 white blood cells and 2,200 red blood cells per cubic millimeter; total protein, 90 mg. per cent; and sugar, 40 mg. per cent.

During the first few months of this hospitalization, the patient's condition gradually improved in that he regained consciousness, talked, and followed a few simple commands. His neurologic status soon reached a plateau, however, and continued substantially the same throughout the remaining years of life.

He was disoriented, belligerent, and resistive to examination and nursing care. He exhibited an impaired understanding of commands, and his conversation was characterized by echolalia; profanities; or childish, stereotyped productions. The remainder of the neurologic examination revealed diffuse pallor of the optic disks, left homonymous hemianopsia, left-central facial paresis, dysarthria, left hemiparesis, left-sided hyperreflexia, and increased resistance to passive movements of all limbs. Although he was frequently placed in a wheel chair, most of his time was spent in bed, and he required complete nursing care.

Seizures continued throughout the course despite the administration of anticonvulsants. In the first year of hospitalization, these consisted mainly of generalized clonic convulsions with deviation of head and eyes to the left, occurring singly or in series at a frequency varying from 3 per month to 1 every two months. For two years, they decreased

SEROLOGIC STUDIES FOR HERPES SIMPLEX

Date of serum	*Day of illness*	*Herpes simplex complement-fixation test*	*Herpes simplex neutralization studies*
7/ 6/53	15	Positive in 1:64 dilution*	Positive
8/ 4/53	44	Positive in 1:16 dilution*	Not done
8/24/53	65	Positive in 1:16 dilution*	Positive
11/12/53	144	Positive in 1:8 dilution	Not done
11/23/53	155	Positive in 1:16 dilution	Not done

*Results of 3 separate tests

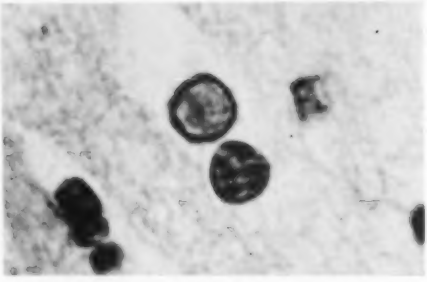

Fig. 1. Two oligodendroglial nuclei are shown. The upper one contains an eosinophilic intranuclear inclusion body and shows margination of the nuclear chromatin. Surgical specimen (first operation). Hematoxylin and eosin stain. × 950

in frequency and severity. During the last year of life, there were frequent focal seizures characterized by clonic movements of the left upper extremity and jaw, commonly without any impairment of consciousness. Two electroencephalograms were made. The first one, in 1955, was interpreted as normal. The second one, in 1958, less than one month before death, was abnormal, depicting an impaired state of consciousness with seizure discharges independently in both cerebral hemispheres.

During most of his hospitalization, the patient's temperature was normal except for occasional elevations in the course of intercurrent infections. Roentgenograms of the chest revealed pulmonary infiltration, which was thought to represent chronic inflammatory disease of the lungs secondary to repeated aspirations.

Two additional lumbar punctures were performed in this hospital. One, in 1955, under sedation with Sodium Amytal revealed a clear, colorless fluid under a pressure of 35 mm. containing 2 lymphocytes and 4 crenated red blood cells per cubic millimeter; total protein, 125 mg. per cent; and normal sugar and chloride content. The other, in 1958, yielded a clear, colorless, acellular fluid under a pressure of 80 mm.; total protein, 139 mg. per cent; and normal sugar and chloride content.

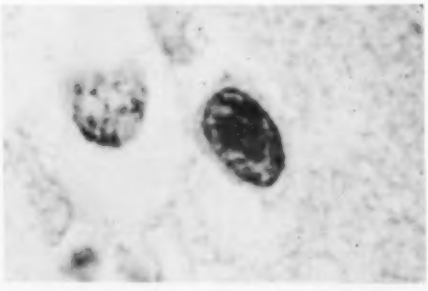

Fig. 2. A small neuron with an eosinophilic intranuclear inclusion body. Surgical specimen (first operation). Hematoxylin and eosin stain. × 950

During the last months of life, the patient became lethargic and periods of singultus, episodes of vomiting, and frequent temperature elevations developed. Finally, he became cyanotic and comatose and died on March 9, 1958, four years and eight and one-half months after the onset of the illness.

General autopsy findings. The immediate cause of death was a severe, bilateral, exogenous lipoid pneumonia of the aspiration type associated with an acute bronchiolitis and tracheobronchitis. The liver and spleen showed acute and chronic congestion. The kidneys were the site of a moderate segmental chronic pyelonephritis and the urinary bladder revealed chronic cystitis. The heart, adrenals, thyroid, and pituitary were negative. No inclusion bodies were found in any of the viscera.

NEUROPATHOLOGIC FINDINGS

Microscopic findings of surgical specimens. The specimen derived from the first needle biopsy of the right temporal lobe on June 25, 1959, showed edematous rarefaction, petechial hemorrhage, eosinophilic degeneration of neurons, mild diffuse increase in microglia cells, hypertrophy of endothelial cells of some of the small vessels, and a mild perivascular infiltration by polymorphonuclear leukocytes. There were rare foci of more advanced tissue necrosis infiltrated with microglial cells and macrophages. Rarely, characteristic eosinophilic intranuclear inclusion bodies were found in the oligodendroglia (Fig. 1), astrocytes, and degenerating neurons (Fig. 2). The inclusion-bearing nuclei showed peripheral margination of the chromatin substance and a relatively clear space about the inclusion. The identity of some of the inclusion-bearing glial cells was difficult to establish. Subsequent biopsy specimens from the right temporal and occipital regions showed essentially similar features, the inclusions being found more frequently.

In sections from the right temporal lobe at the time of the decompressive procedure on June 29, 1953, changes were essentially similar to those previously described except that necrosis was more advanced and microglial proliferation more active (Fig. 3). The leptomeninges were infiltrated by polymorphonuclear leukocytes and red blood cells.

Gross description of the brain after fixation. The right temporal lobe, the ventral portion of the right parietal lobe, and the entire right occipital lobe had been previously resected, resulting in marked asymmetry of the specimen. The dura of this region, some fat, and a small segment of

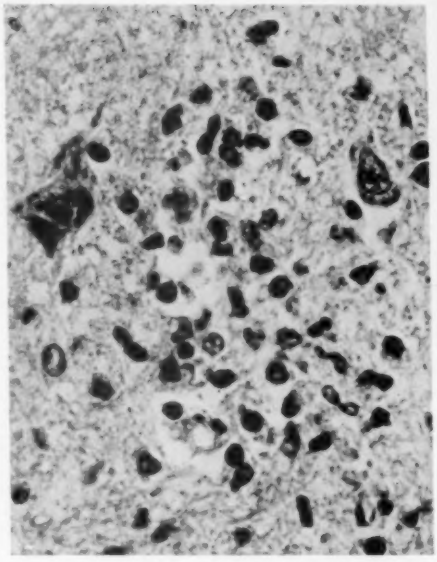

Fig. 3. Focal nodular proliferation of microglial cells in cortex. Surgical specimen (second operation). Hematoxylin and eosin stain. × 430

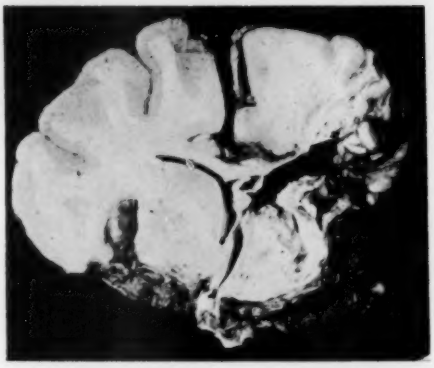

Fig. 4. Coronal section through frontal lobes. In addition to involvement of right inferior and middle frontal gyri and lateral aspect of right basal ganglia, the cingulate and orbital gyri, gyri recti, and islands of Reil show roughly symmetrical, spongy, malacic degeneration.

cranium were retracted into the resulting concavity and were firmly adherent to the neighboring thickened leptomeninges. There was also firm adherence of the right tentorial leaf to the residual leptomeninges of the right middle fossa.

The borders of this defect, which included the caudal segment of the inferior frontal gyrus, the ventral extremity of the right pre- and postcentral gyri, the ventral half of the right superior parietal lobule, and the ventral portion of the right cuneus were soft, shrunken, and distorted. In addition, the caudal two thirds of the right gyrus rectus and immediately adjacent portion of the orbital gyrus were shrunken and light brown in color. The remainder of the right orbital surface was collapsed into a formless, light brown tissue adherent to the inner surface of the dura. Similarly, the left gyrus rectus and adjacent orbital gyri, the cingulate gyri, and paraolfactory areas were diffusely softened, shrunken, and light brown in color. The dorsal aspect of the corpus callosum, the left uncus, and the hippocampal gyrus were soft, spongy, and discolored a light brown.

The remainder of the cerebral cortex was of normal contour, consistency, and color. The optic chiasm and nerves and other cranial nerves showed no gross abnormalities. The arteries at the base of the brain were normal in distribution, average in caliber, and showed only very rare, discrete, yellow, mural opacities. There were no external abnormalities of the brain stem except for a slightly shrunken right cerebral peduncle and pyramid. No changes were noted in the cerebellum externally.

Sections of the cerebrum confirmed the presence of destructive lesions corresponding to the areas referred to externally. The most severely affected were the right gyrus rectus and adjacent orbital gyri, which had been reduced to a narrow ribbon of collapsed, fibrous, brown or light brown tissue interposed between the thickened leptomeninges and the ventral wall of the anterior horn of the right lateral ventricle, the latter showing a focal, ventral dilation. The white matter immediately lateral to the rostral portion of the right corpus striatum and adjacent inferior frontal gyral and central frontal white matter (Fig. 4) appeared as a soft, spongy, light brown, fibrous tissue. The parolfactory areas were contiguously involved with total loss of the normal architectural features. The posterior portion of the left gyrus rectus and adjacent orbital gyri were similarly affected. These bilateral lesions of the ventral surfaces of the frontal lobes extended posteriorly to involve the insular cortex, extreme and external capsules, claustrum, and the lateral margins of the putamen on the one hand and the cingulate gyri on the other. On the right side, the lesion was contiguous with the tissue defects attributable to the surgical procedures previously described. The body of the corpus callosum measured only 1 to 2 mm. in thickness. The posterior portion of the right corpus striatum and most of the right thalamus had been totally destroyed or removed. The right lateral ventricle communicated with the deep

Fig. 5. Photomacrograph of cingulate gyri which are reduced to loose, glial scar tissue. Pallor of superior frontal gyral white matter is notable. Fornices are shrunken and almost completely demyelinated. Weil myelin stain

defect in the right parietal region. The caudal left frontal and parietal white matter contained poorly defined, slightly retracted, microcystic, yellowish-gray, softened areas. Similar lesions were noted in the cortex in the left interparietal sulcus and in the adjacent white matter of the superior and inferior parietal lobules. The left hippocampus, amygdaloid nucleus, and uncus were almost totally destroyed. The right cerebral peduncle, pontine base, and pyramid were atrophic. The cerebellum was not remarkable on section.

Virologic study of a brain section removed at necropsy was negative.

There was focal adhesion of the thickened spinal leptomeninges to the inner surface of the dura. The nerve roots showed no gross abnormalities. There was slight pallor of the lateral columns of the cord, particularly on the left side.

Microscopic examination of the brain. The zones bordering upon the resected portions of the brain showed nonspecific encephalomalacia and gliosis. No inclusion bodies were noted. The altered areas not ascribable to the operative intervention showed a fairly uniform appearance, varying only in intensity. The cingulate gyri (Fig. 5) were totally involved and were converted into a loose-meshed mass of gliosis with no remaining neurons (Fig. 6). There was a prominence of small blood vessels in the involved areas. The adjacent frontal cortex was also affected, occasionally showing a laminar degeneration. The overlying leptomeninges showed a slight increase in connective tissue fibers and infiltrating lymphocytes. Adjacent white matter, including the dorsal portion of the corpus callosum, was rarefied and showed an increase in astrocytes. No inclusion bodies were found. In the posterior portions of the right gyrus rectus and the orbital gyri, and in both parolfactory areas, tissue destruction was more complete (Fig. 7) and gliosis more intense. There were many cystic spaces between bands of dense fibrillary gliosis containing lymphocytes and rare macrophages. Groups of ferruginous, shrunken remnants of nerve cells were present in the glial scar. More rostrally, the changes were less intense and were often confined to the white matter. The lateral wall of the anterior horn of the right lateral ventricle was largely denuded of ependymal cells and contained an increased number of astrocytes and their fibers with many embedded ependymal cell clusters. The extreme and external capsules and each claustrum, the lateral portions of the putamens, and the superior and inferior lips of the left Sylvian fissure (Fig. 8) exhibited similar histologic lesions to those previously described. The central white matter of the posterior extremity of the left frontal lobe and the anterior portion of the parietal lobe showed rarefaction, gliosis, and numerous malacic cysts, which were traversed by small numbers of blood vessels and contained a few macrophages and lymphocytes. Many remaining nerve fibers in this area showed irregular swelling. Small cystic lesions of the left parietal cortex revealed similar histologic features. In all of these lesions, many of the astrocytes had brown pigment on the surface of their cell bodies. The left hippocampal gyrus

Fig. 6. Superficial layers of right cingulate gyrus (right side), composed largely of hypertrophied astrocytes and their fibers, form a loose meshwork. Leptomeninges (left) are mildly thickened. A few scattered lymphocytes are seen in the cortex. Hematoxylin and eosin stain. × 430

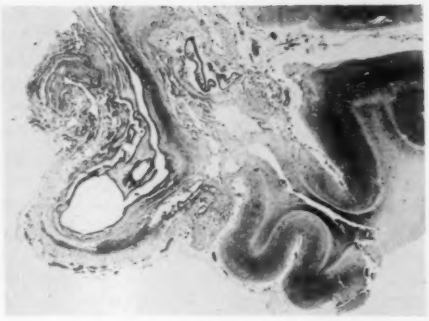

Fig. 7. Photomacrograph of ventral aspect of right frontal lobe showing extensive destruction and scarring of the paraolfactory area, gyrus rectus, and adjacent portion of the orbital gyri. Lateral ventricle shows a ventral out-pouching. Weil myelin stain

and hippocampus, which were reduced to a narrow fibrous band (Fig. 8), were seen as linear cystic spaces sparsely traversed by small blood vessels. These spaces contained small numbers of lymphocytes and were bordered by narrow, subpial and subependymal glial scars. A few ferruginous neurons were seen in the marginal scars. A large portion of the temporal white matter was rarefied and gliotic. The remaining portions of the putamen and globus pallidus showed no unusual features bilaterally. The left thalamus showed a diffuse loss of neurons and a marked fibrillary gliosis. The lateral portion of the right optic nerve showed a marked loss of myelinated fibers, an irregular swelling of the remaining fibers, and an isomorphic gliosis. The left optic nerve also showed a mild gliosis in its medial portion. The basal leptomeninges exhibited proliferation of connective tissue cells and fibers and an infiltration by small numbers of lymphocytes, monocytes, and fewer polymorphonuclear leukocytes.

There was a marginal gliosis in the midbrain. The right corticospinal tract within the brain stem showed a diminution of its axons and an associated gliosis. No appreciable changes were present in the left corticospinal tract. A granular ependymitis was present in the aqueduct and fourth ventricle.

Within the cerebellar folia was a diffuse loss of Purkinje cells associated with a proliferation of Bergmann's astrocytes. The granular layer was slightly rarefied with an equivalent astrocytosis.

There was a slight to moderate increase in connective tissue fibers in the spinal leptomeninges, but no inflammatory changes were noted. The spinal cord showed a marked and well-defined degeneration and gliosis of the left lateral and right anterior columns. The right lateral column also showed similar changes, but they were less extensive and less clearly defined.

Fig. 8. Photomacrograph of left temporal lobe and insula demonstrating fairly discrete involvement of extreme and external capsules, claustrum, lateral portion of putamen, inferior lip of Sylvian fissure, amygdaloid nucleus, hippocampal gyrus, and hippocampus. Weil myelin stain

DISCUSSION

In a comprehensive review of acute encephalitis with nuclear inclusions in adolescents and adults, Haymaker and associates[9] have presented the symptomatology, neurologic signs, and pathologic features. There were 7 patients from whose brains the herpes simplex virus was isolated and 30 patients whose clinical and neuropathologic features closely resembled those of the proved cases. Two cases occurred in the second decade of life, nearly half of the cases in the third decade, and distribution of cases was fairly even in the fourth, fifth, and sixth decades. The du-

ration of illness ranged from five days to three and one-half months. The authors also included our case, which lasted four and two-thirds years. In about 70% of the cases, the duration was two weeks or less. In most instances, the onset was acute with headache, nausea, vomiting, sore throat, fever, chills, an organic mental syndrome, and disturbances in the state of consciousness as early manifestations. There were stiffness of the neck and evidence of unilateral or bilateral pyramidal tract involvement. Seizures of various types were commonly observed, and, later in the course of the illness, spasms and hyperkinesis were noted. Less commonly, cranial nerves were involved. The cerebrospinal fluid often showed an elevated pressure; pleocytosis and an increased total protein content were found in most cases.

Haymaker and associates[9] also described the neuropathologic features of acute inclusion encephalitis of herpetic type. There is a constant and extensive hemorrhagic softening of the temporal cortex and subcortical white matter, including the hippocampal formation and amygdaloid nuclei. The process frequently involves the occipital lobe, insular region of the frontal lobe, cingulate gyrus, and posterior orbital gyri. The lesions are often bilateral but usually more extensive on one side than on the other. The microscopic changes include degeneration of nerve cells, astrocytes, and oligodendroglia. The necrotic area becomes filled with macrophages and the overlying leptomeninges and perivascular spaces of the less severely affected areas show lymphocytic and macrophage infiltration. Characteristic type A, intranuclear, eosinophilic inclusion bodies are found in the affected neurons and oligodendroglia of the cortex and white matter in the necrotic foci or adjacent tissue in the early stage and in the vicinity of large confluent areas of tissue breakdown in the later stages. Haymaker and associates[9] report cytoplasmic inclusions in only 2 of their cases. In the later stages, marked astrocytosis in the uppermost lamina occurs, and enlarged astrocytes are seen throughout the cortical laminae. Other parts of the brain, including thalamus, hypothalamus, basal ganglia, and pons, may be involved but much less consistently.

In infancy, there are 2 types of central nervous system infections caused by the virus of herpes simplex: (1) disseminated disease, the principal changes being hepatoadrenal necrosis and (2) infections largely restricted to the central nervous system. Of the first type, the only virologically proved case we could find was reported by Zuelzer and Stulberg.[8] They also reported 7 probable cases without virologic proof. Haymaker and associates[9] collected 2 cases of disseminated infection with brain involvement but without virus isolation. Of the second type, 3 cases have been reported by Smith, Lennette, and Reames,[4] Wildi,[7] and Ginder and Whorton.[2] Of all the cases of proved herpes simplex encephalitis in infancy, only 2 [7,8] had herpetic skin lesions.

Comparing the case presented here with those of proved herpes simplex encephalitis, we find many similar features. The age at onset of the illness, 20 years, corresponds with the range in other reported cases. The mode of onset was acute, consisting of an organic mental syndrome and fever. This was rapidly followed by coma, nuchal rigidity, and clinical evidence of involvement of the right cerebral hemisphere. Tremors also developed. All of these clinical manifestations have been observed commonly in the proved cases. Another important and striking similarity between our case and the others is the cerebrospinal fluid examination, which revealed an elevated pressure, pleocytosis, and an increase in the total protein content. Although the duration of the patient's life after onset of the disease was much longer than that found in the proved cases, it should be emphasized that 2 intracranial operations were performed; during the second of these, a large amount of brain was removed, which resulted in a substantial decompression. In addition to this, supportive treatment consisting of antibiotic and anticonvulsant drugs and excellent nursing care also contributed to the protracted course. While it is difficult to say when the active phase of the infection stopped, especially in view of the intervening bacterial meningitis, it seems reasonable to believe that the primary infection became inactive soon after the onset. This may account for failure to isolate a virus from the cerebrospinal fluid and brain tissue on the one hundred and thirty-sixth day of the illness.

From the pathologic viewpoint, there are definite similarities between our case and those

of herpes simplex encephalitis found in the literature. The topography of cerebral involvement, which included the ventral aspects of the frontal and temporal lobes, corresponds closely with that found in other reported cases. At the time of the craniotomy, moreover, which was performed during the acute phase of the illness, the brain appeared softened and there were multiple hemorrhagic areas, which are characteristic features of herpetic encephalitis. Another similarity is that, although the lesions were bilateral, there was greater involvement on one side. The microscopic findings in the biopsy specimens were typical of those described by others.

There are many reports[9,15–29] in the literature of cases in infancy and adulthood which resembled proved herpes simplex encephalitis clinically and pathologically except that inclusions were found in some and not in others. In the vast majority of instances, virus isolation and identification either had not been attempted or were negative. In the few cases in which the herpes simplex virus was isolated, inclusions were not found. Such cases do not fill essential criteria for a definite diagnosis.

Since our case was once reported by Kurtzke[13] as an instance of subacute inclusion encephalitis of the type described by Dawson,[30,31] we shall point out the main features of this condition and compare our case with it. A review of the literature discloses at least 25 autopsied cases.[9,28,32–37] Although there are some similarities, there are rather distinct differences, both clinically and pathologically, between acute and subacute inclusion encephalitis. Whereas the former affects infants and adults, the latter affects children almost exclusively, with the exception of Krücke's[28] case 9 and 1 patient in the series of Haymaker and associates,[9] both patients being in the fourth decade of life. Characteristically, subacute inclusion encephalitis of the Dawson type has an insidious onset, mental symptoms being among the earliest to appear. There may be seizures and stereotyped jerkings of one or more limbs. The acute febrile onset with signs of meningitis, commonly seen in herpetic encephalitis, is not usually observed in subacute inclusion encephalitis. Gradually, a profound dementia develops, and there may be evidence of decortication. Fever may occur during the course of the illness. The usual duration of the illness, which ends fatally, is from two to six months; several cases have been reported which lasted even longer.[28,34,35,37,38] Ordinarily, the cerebrospinal fluid either is normal or shows a slight pleocytosis.

From the pathologic viewpoint, instead of massive necrosis of large cortical and subcortical areas as seen in the acute form, Dawson's type of subacute inclusion encephalitis is characterized primarily by a polioclastic process involving the cerebral cortex more or less diffusely, the nuclei of the upper and lower brain stem, and, occasionally, the spinal cord. The topography of the cortical involvement in some cases of the subacute form, however, closely resembles that seen in the acute form. Microscopically, there are neuronal changes ranging from chromatolysis to complete disappearance and frequent neuronophagia; perivascular infiltration by lymphocytes and plasma cells; microglial hyperplasia, often in the form of rod cells; and astrocytosis resembling general paresis. The acidophilic inclusion bodies, both intranuclear and intracytoplasmic, are more hyaline than those in acute inclusion encephalitis, the latter tending to be more granular. The inclusion bodies in the subacute form may be multiple and small and often become coalescent. Typically, the white matter alterations are mild and can be accounted for by neurocytolysis or spread of inflammation into the subcortical zones.[34]

There are, however, cases in which the white matter involvement is more extensive, and these closely resemble the subacute sclerosing leukoencephalitis originally described by van Bogaert,[39] which is clinically indistinguishable from subacute inclusion encephalitis. Eosinophilic intranuclear inclusion bodies have also been noted in some cases of subacute sclerosing leukoencephalitis.[9,28,34,37,40–47] Although Brain, Greenfield, and Russell[33] consider their cases of subacute inclusion encephalitis of Dawson type to be different from van Bogaert's[39] subacute sclerosing leukoencephalitis, Haymaker and associates[9] believe these conditions are the same disorder with a rather wide spectrum of pathologic changes.

Comparing the case reported here with those of subacute inclusion encephalitis of Dawson type, we find that our patient exhib-

ited an acute onset with fever, meningeal signs, and coma or stupor in the early phase of the illness, which is more in keeping with acute than subacute inclusion encephalitis. Although the protracted survival of more than four years in our patient might seem to indicate a similarity to the subacute form, we wish to emphasize that the two craniotomies apparently produced effective decompression in the acute stage and that supportive therapy enabled the patient to survive for some time after the infection had ceased to be active. The cerebrospinal fluid findings in this case do not resemble those reported by Dawson[30,31] and subsequent authors. At postmortem examination, there was no evidence of a persistent inflammatory process in the brain tissue, which is seen in the subacute form.

Opinion is divided regarding the relationship between the acute and subacute form of inclusion encephalitis. It seems advisable, as Peters[47] pointed out, to retain the separation of these groups at the present time, despite certain similarities, until a clarification of the identity of the etiologic agent or agents is achieved, since only the composite of pathomorphologic changes, their localization, and the clinical syndrome can lead to the establishment of nosologic entities in the lack of such etiologic knowledge. Peters[47] and others agree with the point stressed by Seitelberger[48] that the mere presence of the inclusion bodies which are nonspecific in nature cannot be relied upon as a criterion in classifying cases.

While it seems generally agreed that the *cytoplasmic* inclusions seen in viral infections are frequently directly related to respective virus particles, the relationship of *intranuclear* inclusions to "elementary bodies" is still controversial and not conclusively determined as yet.[49] In experimental studies of herpes simplex infection, it has been shown that, in the early stages, the nucleus of an infected cell contains a basophilic, Feulgen-positive material, which fills and swells the nucleus as the chromatin is marginated. At this stage, many virus particles are revealed within the nucleus by electron microscopic examination. A small, rounded eosinophilic body remains in the center of the nucleus in the wake of the Feulgen-positive material, which subsequently diminishes and finally disappears. This corresponds to the typical inclusion body of Lipschütz.[50] Barski and Robineaux[51] recently concluded from their phase contrast microcinematographic study that the typical herpes inclusion body visible in a fixed preparation should be regarded as the result of physicochemical changes in the nucleoplasm rather than as a restricted site of virus formation or accumulation. The eosinophilic inclusion of herpes simplex is then believed to be the end stage of the process, and to be a nonspecific change, for identical inclusion bodies are also seen in nonviral diseases.[50,52]

Certain aspects of the virologic studies performed in the case presented here deserve comment. Attempts to isolate a virus from cerebrospinal fluid and brain were made but failed. This failure, however, might be attributed to the late collections of specimens when the disease process was probably no longer active. The herpes simplex complement-fixation test (see table), which was first performed on the fifteenth day of the illness, was positive in a dilution of 1:64 and twenty-nine days later showed a fourfold decrease in titer. The herpes simplex neutralization test was positive on the fifteenth and sixty-fifth days of the illness. An acute phase serum at the onset was not tested by either of these methods. Hayward[53] reported that the results of testing for antibody against four strains of herpes simplex virus showed close agreement of complement-fixation and neutralization technics. Rivers and Horsfall[54] and Gajdusek, Robbins, and Robbins[55] agree that antibodies to the virus of herpes simplex appear about the fourth day after the onset of the primary infection. Afzelius-Alm,[12] on the other hand, states that the antibodies do not appear within the first ten days after the acute onset but are detectable two to three weeks later. Since the former group of authors reported instances of cutaneous herpes and Afzelius-Alm reported those of presumably primary herpetic meningoencephalitis, one wonders whether this difference in findings may not be due to the site of the primary infection—skin or nervous system. In any event, there is general agreement that an increase in complement-fixing antibody titer of fourfold or more between the acute and convalescent phase sera is compatible with a primary infection by the virus of herpes simplex.

Although Dodge and Cure[14] may be correct in thinking that the decrease in antibody level is *highly suggestive* of a recent herpetic infection, no further conclusions can be drawn. From the serologic tests in our patient, we may conclude that at one time he was infected with this virus, but it cannot be definitely incriminated as the cause of the encephalitis.

In conclusion, we believe that the clinical, laboratory, biopsy, and postmortem findings in this case point to an acute inclusion encephalitis of herpes simplex type rather than the inclusion encephalitis of Dawson type. It is noteworthy that Haymaker and associates[9] and Dodge and Cure[14] also classified the disease in our patient as one of acute inclusion encephalitis of herpes simplex type. However, since the virus of herpes simplex was not isolated and since the serologic tests were inconclusive, a definite diagnosis cannot be made.

SUMMARY

The clinical, laboratory, and postmortem findings of a case of acute inclusion encephalitis diagnosed by brain biopsy have been described. Though no etiologic agent was isolated, reasons have been given for believing that the encephalitis was of herpes simplex type.

We wish to express our gratitude to Dr. Abner Wolf for his guidance and helpful suggestions in the preparation of this work. We also thank Dr. Webb Haymaker for allowing us to review the slides of his biopsy specimens.

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Water intoxication following intracranial surgery

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THE METABOLIC RESPONSE after any type of trauma usually includes retention of water. This portion of the metabolic reaction has been attributed to release of antidiuretic hormone from the posterior pituitary gland. Retention of water without equivalent retention of electrolytes results in hypotonicity of body fluids. When this occurs with sufficient rapidity and to a significant degree, clinical water intoxication occurs. The manifestations of this syndrome are almost entirely neurologic and are related to changes in hydration of the brain.[1] The syndrome includes drowsiness, confusion, seizures (focal or generalized), coma, and intracranial hypertension.

This report describes observations of salt and water metabolism in patients undergoing neurosurgical operations. The purpose is to determine the susceptibility of these patients to water intoxication. Hypoosmolality is of twofold importance: the signs are primarily neurologic, and the imbalance probably arises from disturbed intracranial (pituitary) function. Although water balance and intoxication have been thoroughly studied after other types of trauma, there has been little investigation of the response to intracranial injury and surgery. That water retention does occur after neurosurgical procedures is demonstrated by the direct relationship between intake and balance in a selected series of 12 patients who had constant intake of sodium in the posttraumatic state (Fig. 1). On the other hand, there is no relationship between sodium and water balances, indicating that water retention is not dependent on salt conservation alone. It is also noteworthy that, in this group of patients, the water retention could not be related to the degree or location of intracranial trauma.

Water intoxication was first described by Rowntree in 1926.[2] He attributed the symptoms to cerebral edema. Several reports have appeared concerning the hazard of water intoxication after general surgical procedures which are accompanied by liberal administration of fluids low in electrolyte concentration.[3–5] The clinical syndrome has been repeatedly and adequately described. Recently, Crawford and Dodge[6] have called attention to the syndrome in relation to neurologic disease in the pediatric age group. These authors have also performed valuable studies on experimental water intoxication in animals in an attempt to delineate the physiologic mechanisms involved.[7,8]

METHODS

A group of 10 patients was selected for study from the neurosurgical services of Cincinnati General and Veterans Administration hospitals. These patients were, with 1 exception, undergoing elective intracranial surgery. No attempt was made to select patients on the basis of age or general state of health except to exclude any with disease known to affect significantly water or electrolyte metabolism.

No specific preoperative nutrition was employed. During the operative and postoperative periods, no sodium chloride was administered. Daily intake of 2,000 to 4,000 cc. of glucose solution was given, the average being less than 3,000 cc. The withholding of salt represented a deliberate challenge to the pa-

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Fig. 1. Observations on 12 postoperative neurosurgical patients showing direct relationship between water intake and balance and absence of relationship between water and sodium balances

tients to determine susceptibility of neurosurgical patients to intoxication under conditions of parenteral nutrition commonly employed. The intake was recorded, and all urine output was collected and recorded; aliquots were preserved for analysis.

The patients were carefully observed for clinical evidence of intoxication—increasing drowsiness or seizures during the first three postoperative days. If such signs appeared, the patient was immediately given a saline infusion. If the signs appeared to be reversed by sodium chloride and were accompanied by lowering of the serum sodium, a diagnosis of water intoxication was made. The study was discontinued at any time the patient had a postoperative diuresis as it was apparent that water intoxication would not occur under such circumstances. Standard methods of chemical analysis were used.

OBSERVATIONS

Observation on 10 patients, undergoing 11 operative procedures, are summarized in the table. There were 4 instances of unmistakable water intoxication; 3 other patients demonstrated signs which were interpreted as mild intoxication, and the remaining individuals showed no evidence of water imbalance.

All patients who became intoxicated did so within a period between forty-eight and seventy-two hours postoperatively. It appears, therefore, that this represents the hazardous

SUMMARY OF CLINICAL, BALANCE, AND LABORATORY DATA ON PATIENTS UNDER INVESTIGATION

Patient	Age	Diagnosis	Water intoxication	Days to intoxication	Na balance (mEq. per 70 kg.)	Cumulative H_2O balance* (cc. per 70 kg.)	H_2O balance* first day (cc. per 70 kg.)	% Change serum osmolality	Change serum sodium (mEq. per liter)
A. H.	65	Metastatic cerebral tumor	XX	3	− 58.7	6,895	1,855	−12.7	138 → 120
F. M.	49	Cerebral glioma	XX	3	−132.3	4,039	1,575	−12.6	146 → 122
J. I.	60	Carcinoma of mouth	XX	2	−203.0	2,884	1,281	−8.6	142 → 128
H. H.	68	Cerebral glioma	XX	2.5	+ 24.9	5,077	4,411	−14	140 → 120
C. C. No. 1	50	Metastatic cerebral tumor	X	2	− 77.0	3,724	1,673	−8.1	145 → 133
W. D.	48	Cerebral glioma	X	2.5	− 50.7	2,408	1,372	−9.7	150 → 135
J. McQ.	27	Cerebral glioma	X	2	−173.6	3,115	3,010	−8.4	144 → 132
T. W.	42	Intracerebral hematoma	0	–	−135.2	1,183	1,183	−6.2	141 → 132
P. T.	30	Gunshot wound	0	–	−168.9	4,984	1,666	−0	? → 139
A. S.	67	Cerebral glioma	0	–	− 68.6	339	339	+3.2	122
C. C. No. 2	50	Metastatic cerebral tumor	0	–	− 15.1	2,569	1,337	−4.8	139 → 131

*Water balance was determined simply as input minus urine output.

period from this standpoint and that any patient who has not become intoxicated by the end of three days is not likely to have symptomatic hypotonicity. The patients who did not become intoxicated had spontaneous diuresis within a period of one to three days.

The patients varied in age from 27 to 68 years. Previous reviews of water intoxication have almost invariably stressed the greater susceptibility in the older age group, probably because of decreased ability to conserve sodium. Of the 4 patients in the present series who became fully intoxicated, 3 were over 60 years of age while the average age of the remaining patients was 44 years.

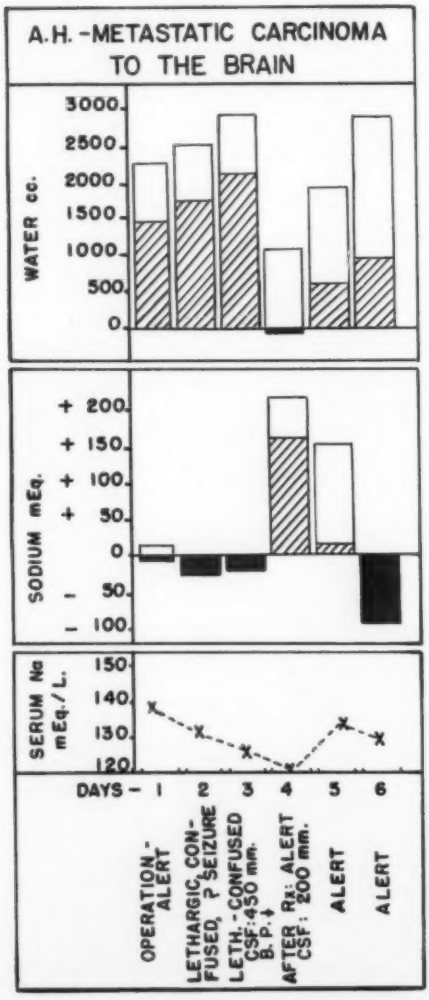

Fig. 2. Patient 1, correlation of metabolic balance with clinical state

No relationship was found between degree of clinical intoxication and the negative sodium balance. The amount of sodium loss is apparently only a measure of the individual ability to retain salt under conditions of salt deprivation. One patient inadvertently received a small amount of salt and, despite a positive balance, became intoxicated. It may be concluded, therefore, that the degree of sodium loss is not an indication of susceptibility to intoxication in the individual patient.

A somewhat closer relationship existed between intoxication and cumulative water balance; 3 of the 4 intoxicated patients retained in excess of 4,000 cc. without allowance for insensible loss. The retention during the first day was not excessive in the intoxicated group, but, apparently, there was present in these patients a stimulus for continued water retention without spontaneous diuresis.

All patients with classic intoxication had a serum sodium less than 130 mEq. per liter. It would appear that the most consistent correlation was between intoxication and the per cent lowering of serum osmolality. Marked intoxication occurred when the change was greater than 10% (1 exception), and mild intoxication occurred with a change of 8 to 9%. These figures correlate well with experimental observations of Dodge, Crawford, and Probst,[8] who noted a 7.5 to 16.1% positive water balance and a 10% increase in brain water in intoxicated animals.

No relationship was found between the type of pathology or the location of the lesion and the occurrence of intoxication. Although only one instance of accidental intracranial injury is included in this series, observations which have been carried out in this clinic indicate that salt and water metabolism after injury follows the same pattern as after intracranial surgery and, therefore, water intoxication might be expected to present a similar hazard.

It is of interest that 3 of the 4 fully intoxicated patients received thiopental during induction of anesthesia. The antidiuretic effect of certain anesthetic agents has been well recognized. Aprahamian,[9] studying the influence of anesthetic agents on water and solute excretion, found that thiopental had no antidiuretic effect of its own and seemed to prevent antidiuresis normally provoked by ether, nitrous oxide, and cyclopropane. We are unable to conclude that thiopental has any preventive effect in the development of water intoxication.

The frequent use of hypertonic urea solutions in neurosurgical practice today raised the question of whether this agent would prevent water intoxication. Patient H.H. in this group became intoxicated after receiving urea, but there was no diuresis accompanying its use; 3 other patients in the series received urea with the usual diuretic effect, and no significant intoxication occurred in these individuals. These observations suggest that urea, if accompanied by diuresis, will probably prevent water intoxication.

It seems worthwhile to review the case histories of the 4 patients who became severely water-intoxicated, with more detailed analysis of salt and water balance.

Case 1. A. H. (V.A.H. No. 12637) was a 65-year-old man (Fig. 2). This patient began to lose weight three months before admission. Two months before admission, he noted numbness of the left arm and leg, followed after several weeks by weakness of these extremities. He had lost 30 to 40 lb. during the illness. His appetite had been extremely poor, but there was no vomiting.

Examination revealed a poorly nourished man with marked loss of cortical sensory modalities over the left side of the body and left hemiparesis with hyperreflexia.

Roentgenograms of the chest showed a mass in the right lower lobe, interpreted as bronchogenic carcinoma. Carotid angiography and air encephalography demonstrated a right parietal mass lesion. Craniotomy was performed, but the lesion was not located. Several days later, reexploration was carried out and a small metastatic nodule was found in the parietal lobe. Thiopental and ether were employed for anesthesia.

Comment. The balance study was carried out after the second craniotomy. The patient was awake on the day of surgery, but his condition deteriorated during the next forty-eight hours, with confusion, lethargy, and seizures.

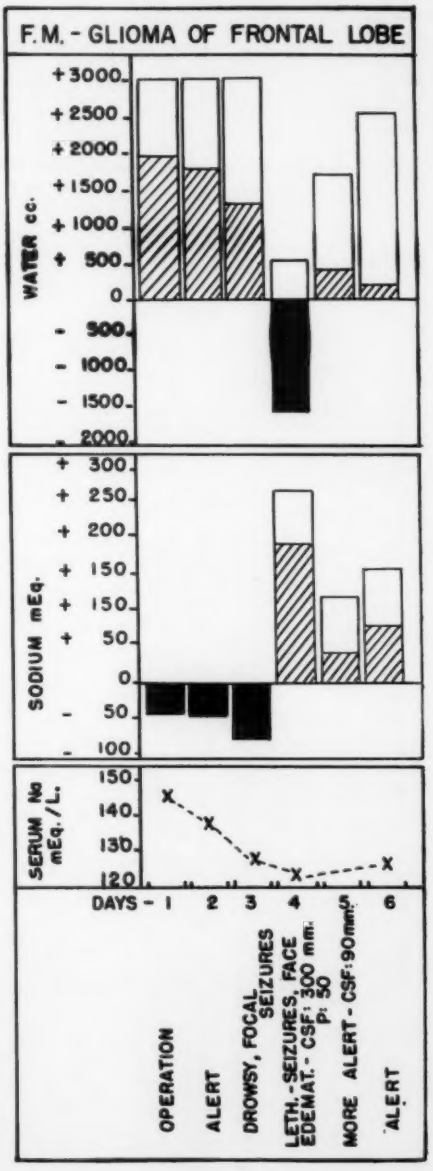

Fig. 3. Patient 2, correlation of metabolic balance with clinical state

After administration of hypertonic saline, there was dramatic improvement in his neurologic state. It is felt that the course could have been easily mistaken for postoperative hematoma formation.

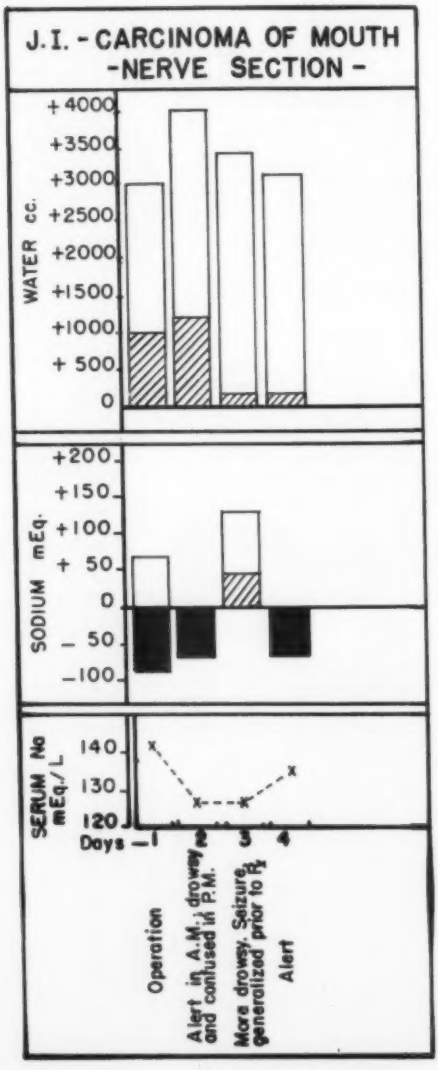

Fig. 4. Patient 3, correlation of metabolic balance with clinical state

During the first three postoperative days, the water intake varied between 2,200 and 2,800 cc., an amount certainly not considered excessive. Except for a small amount given during surgery, there was no salt intake. Allowing for insensible loss of water, approximately 2.5 liters was retained as a result of antidiuretic response. A steady decline of serum sodium occurred.

The patient's state of nutrition was quite poor, and there was probably a significant degree of salt depletion. He had, however, no renal disturbance which prevented salt retention.

Case 2. F. M. (V.A.H. No. 9961) was a 49-year-old man (Fig. 3). The patient had a two-year history of grand mal seizures, which had become more frequent before admission. The seizures began with an aura of a strange taste. The patient had been placed on anticonvulsant medication.

Examination revealed that he was well-nourished. The general physical and neurologic examinations were entirely normal.

Roentgenograms of the skull were normal. Carotid angiography revealed a mass lesion in the left frontal lobe superior and lateral to the corpus callosum. Craniotomy revealed a tumor nodule high in the left frontal lobe. This proved to be an oligodendroglioma. Thiopental, succinylcholine chloride, and nitrous oxide were used for anesthesia.

Comment. The patient was given 3,000 cc. of fluid daily with no salt intake. On the day after surgery, he was awake, but, during the following day, right-sided focal seizures occurred and he became lethargic. Administration of hypertonic saline caused prompt diuresis and was accompanied by retention of nearly all the salt given. The clinical state rapidly improved. There was no evidence of malnutrition, debilitation, or decreased body sodium in this patient.

Of interest in this patient is the increasing sodium excretion despite the progressive lowering of the serum sodium. This probably represents the earliest stage of a salt-wasting state and may be related to body fluid excess.[10,11]

Case 3. J.I. (C.G.H. No. 378017) was a 57-year-old man (Fig. 4). This patient had a squamous cell carcinoma of the gum diagnosed one year previously and received x-radiation therapy to the left jaw. Six months later, carcinoma was still present in the tonsillar fossa, and, shortly afterward, there occurred x-ray necrosis of the

mandible. This was associated with pain of increasing intensity in the jaw, tongue, and roof of the mouth. Because of pain accompanying the process of eating, he had lost considerable weight.

Examination revealed evidence of poor nutrition, enlargement of the liver, and a tender mass in the region of the left mandible.

Surgery was undertaken for relief of pain. Division of the trigeminal, glossopharyngeal, nervus intermedius, sensory fibers of the vagus, and posterior roots of C2, 3, and 4 was performed. Nitrous oxide and ether were employed.

Comment. The postoperative metabolic analysis differs from the previous cases in that retention of water does not appear sufficient to cause true intoxication. It should be noted, however, that there was no ability to retain salt, so that a negative balance of approximately 160 mEq. occurred during the first forty-eight hours. Despite the surgical event, the patient was unable to limit sodium excretion. Thus, the serum sodium fell in spite of minimal positive water balance. This case, therefore, represents an example of intoxication without water excess, probably resulting from renal wastage of electrolyte. The neurologic deterioration which was corrected by administration of salt seems to justify a diagnosis of true water intoxication.

Case 4. H. H. (V.A.H. No. 14113) was a 68-year-old man (Fig. 5). This patient gave a nine-week history of neurologic deterioration. This had begun as a peculiar sensation in his head and progressed to deterioration of vision, inability to walk, and mental disturbance. He was hospitalized elsewhere and transferred to this hospital. A large sacral decubitus ulcer had been present on his original hospital admission.

Examination revealed that he was in extremely poor nutritional state with a large infected sacral ulceration. Neurologically, there was confusion, apparent blindness, papilledema, and left hemiparesis.

Carotid angiography revealed displacement of vessels and a tumor stain in the right parietal region. Craniotomy revealed an infiltrating glioma in the parietal region, and the tumor was partially removed. Thiopental, succinylcholine chloride, and nitrous oxide were employed.

Comment. The patient was given an excessive amount of water inadvertently on the day of operation. Salt restriction had been planned and was carried out except for a small amount of salt administered during the operation. The patient retained nearly all the water given during that day, and, although there was some diuresis on the next day, he was still in a markedly positive balance. During the latter part of the third day, clinical intoxication occurred and salt was administered. The diuresis was delayed until approximately twenty-four

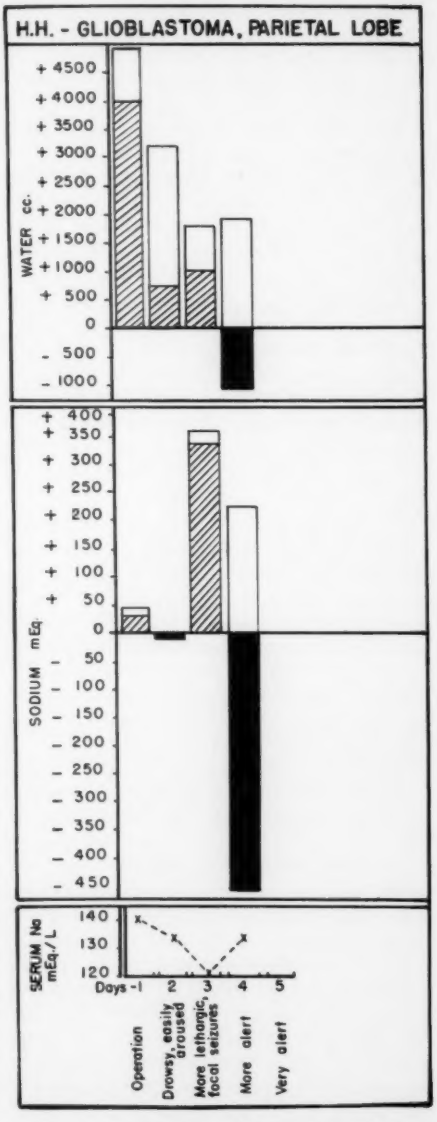

Fig. 5. Patient 4, correlation of metabolic balance with clinical state

hours later, and, at that time, there occurred a large water diuresis accompanied by sodium excretion. Because of diarrhea, the balance study had to be discontinued, but clinical improvement was striking.

The patient was in extremely poor nutritional state throughout. This was reflected in anemia, reversal of albumin:globulin ratio, and obvious physical debilitation. Despite normal serum sodium values preoperatively, it is likely that there was definite sodium depletion.

Points of interest noted in this patient were, first, the lack of diuresis on the day of surgery despite the use of urea. Thus, it seems that the antidiuretic response to anesthesia and surgery in certain instances may be greater than the diuretic effect of urea. It may be noted, however, that the value of urea in dehydrating the brain does not depend on its diuretic effect.

The second point of interest is that this patient was intoxicated despite a positive sodium balance. He was the only patient in this series who had a positive sodium balance at the time of intoxication or discontinuation of the study. A small amount of saline solution was given during operation, and he exhibited a strong sodium-retention response on that and the following two days.

DISCUSSION

The pathologic physiology involved in water intoxication has been the subject of considerable investigation. Yannet[12] produced electrolyte depletion in cats and analyzed the brains, finding that intracellular potassium was released and there was no redistribution of water. Swinyard[13] produced hyponatremia in rats and found that the electroshock seizure threshold was most closely related to changes in extracellular sodium and chloride. The seizure threshold was reduced during the stage of cellular hydration. Woodbury,[14] also working with rats, concluded that hyponatremia does not cause cellular hydration but does increase intracellular sodium and lowers intracellular potassium. He attributes the seizure tendency to these electrolyte changes.

Dodge, Crawford, and Probst[8] have recently made valuable contributions to the physiologic principles involved. By causing excessive hydration in rabbits, they showed the sequence of events in water intoxication: rise of cerebrospinal fluid pressure, slight rise of venous pressure unrelated temporally to cerebrospinal fluid pressure, decrease of electroencephalographic activity frequency and voltage, increase of total body water (both intracellular and extracellular), and decrease of serum osmolality. The electroencephalographic changes could not be reproduced in control animals by artificially raising spinal fluid pressure using an external reservoir and could not be prevented during intoxication by keeping the spinal fluid pressure at normal levels. Thus, the seizure threshold is not related to intracranial pressure. Moreover, the electroencephalographic pattern was improved during treatment with either 15% mannitol or 3% sodium chloride solutions. Both agents produced an increase of serum osmolality, although the levels of both sodium and chloride move in opposite directions with the 2 agents. It was concluded that the seizure activity is not related to levels of sodium and chloride but to changes in total osmolality.

Water intoxication is related to excessive water retention, the pathogenesis of which is not entirely clear but which may be due to inappropriate and prolonged release of antidiuretic hormone. The retained water crosses the blood-brain barrier much more freely than do electrolytes. This results, therefore, in a relative hypertonicity of the fluids of the brain and consequent imbibing of water. The hydration may be intracellular, although this is not proved. The rate of change of osmolality of the body fluids is of fundamental importance; a slow change is much better tolerated than a rapid alteration through the same range.

Water intoxication probably is a greater hazard in neurosurgical practice than in most other fields for several reasons. The state of awareness of the patient is apt to be impaired and the normal thirst mechanisms will therefore not be operative. The normal response to overhydration is one of making water unwanted. If this response is unheeded and the mechanism bypassed by parenteral administration of hypotonic solutions, intoxication is likely. Moreover, it is possible, though certainly not proved, that intracranial injury is more likely to result in a prolonged antidiu-

retic hormone release from the hypothalamico-hypophyseal system than other types of bodily trauma. It is also probable that, while intracranial injury does not render the brain more susceptible to the mechanics of water intoxication, the threshold for clinical manifestations of disturbed salt-water relationships is lowered. Finally, the neurosurgical patient may be in a preoperative nutritional state which predisposes to the development of water intoxication. The frequent occurrence of vomiting predisposes the patient to a state of salt depletion before surgery. Experimental work by Bristol[15] showed conclusively that salt depletion was associated with inability to excrete a water load. Therefore, the individual with hypoosmolality is relatively incapable of handling hypotonic fluids administered postoperatively and is consequently more susceptible to intoxication.

It is of interest that neurologic symptoms are the most prominent manifestations of rapid changes in osmolality of body fluids. This is true whether the change be in the direction of hypertonicity or hypotonicity. Moreover, the symptomatology is nonspecific in character and includes mainly confusion, seizures, and changes in the level of awareness progressing to coma. Because of the necessity to differentiate the condition from postoperative hematoma formation in the neurosurgical patient, it is essential that the surgeon be aware of water intoxication as a possible complication of intracranial surgery.

Excessive hydration should be distinguished from the mild serum hypotonicity which occurs after any trauma or major surgery. This has been termed the "sodium paradox"[16] and is characterized by mild asymptomatic lowering of the serum sodium associated with a low urine sodium. The total body sodium is not altered. The level of serum sodium rarely falls below 130 mEq. in contrast to the greater lowering which occurs in water intoxication. The exact mechanism of postoperative hyponatremia is not understood, but it should not be interpreted as a need for extra sodium replacement.

Treatment of water intoxication consists of limitation of water and administration of sodium chloride. Although there is not necessarily a state of sodium chloride deficit in the body, it is necessary to raise the osmolality rapidly to relieve the neurologic state due to hypotonicity. This is best accomplished by administering hypertonic sodium chloride solution. In the average adult with intoxication, infusion of 300 cc. of 3% sodium chloride solution will usually immediately reverse the neurologic picture. It should be noted that it is not necessary to replace all the sodium needed to restore normal tonicity in order to improve the clinical state. Administration of sodium chloride will initiate a diuresis which then corrects the overhydration. Mild cases of intoxication may be treated simply by withholding water and allowing the normal insensible loss to restore water equilibrium.

Dodge, Crawford, and Probst[8] have pointed out that mannitol or urea solutions might be preferable for treatment in some instances. These agents are effective in raising tonicity and correcting symptoms despite further lowering of serum sodium and chloride. In situations in which the total body sodium and chloride are already increased (for example, congestive heart failure and cirrhosis), these substances may be used for treatment.

Regardless of whether hypertonic sodium chloride or other agents are used to raise osmolality, it is necessary that water administration be limited. This is true because of the occasional patient who will continue to retain water, probably due to sustained inappropriate release of antidiuretic hormone. Under such circumstances, a secondary physiologic mechanism comes into play. The volume receptor mechanism of the body inhibits sodium retention and the result is excessive loss of salt in the urine despite hyponatremia. This is the basis of the so-called "salt-wasting" syndrome, the earliest stage of which was seen in one of our patients (F.M.). The "salt-wasting" state, therefore, is probably secondary only to continued antidiuresis and is correctible only by limiting water intake.[17,18]

Lumbar puncture has no role in the treatment of water intoxication. The intracranial pressure is characteristically elevated but, as demonstrated by Dodge and associates,[8] this is a secondary effect of intoxication and relieving the intracranial hypertension does not alter the neurologic defect.

Management of seizures during intoxication

warrants discussion. The seizures occurring in our patient were successfully treated with usual dosages of barbiturates. Dodge and associates[8] have noted that barbiturates resulted in profound electroencephalographic effects in the presence of experimental water intoxication and cautioned about their use. Recently, Swanson[19] has recommended the use of acetazoleamide (Diamox) for treatment of seizures resulting from water excess. The author demonstrated that acetazoleamide raises the seizure threshold during hypotonicity, presumably by interfering with carbon dioxide transport and thereby altering the extracellular-intracellular sodium ratio. We have had no experience in use of this drug under such circumstances.

Prevention of water intoxication in neurosurgical patients seems preferable to diagnosis and treatment. Prevention can probably be easily achieved by routine administration of salt in the postoperative or posttraumatic period. It may be recalled that intoxication always occurs within the first three days. Because of confusion with peripheral edema, there has been a tendency to restrict or abolish salt from supportive parenteral fluids in an attempt to prevent "cerebral edema." The mechanisms described above suggest that brain swelling is considerably more likely to occur if salt-free fluids only are administered. Since the basic physiologic aberration responsible for water intoxication is a relative excess of water, salt intake will preclude development of hypotonicity. This is particularly true in older individuals who may have greater difficulty in salt conservation. The frequent occurrence of water intoxication in this age group has been noted. It is recommended, therefore, that, during normal posttraumatic parenteral support, the patient be given at least 4.5 gm. of salt (500 cc. of 0.9% sodium chloride solution). In addition, water administration should not be excessive and should be mildly restricted during the first three days after surgery or injury.

SUMMARY

Susceptibility to water intoxication was determined in 10 neurosurgical patients studied during the postoperative period. Salt-free fluids were administered. Severe intoxication was seen in 4 patients, while 3 others had mild symptoms of hypotonicity. The pathogenesis of this disorder is discussed. The factors which are probably responsible for its occurrence in neurosurgical patients are presented. The syndrome may be easily confused with postoperative intracranial hematoma. The means of prevention and treatment, mainly by salt administration, are described.

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A syndrome clinically resembling amyotrophic lateral sclerosis following chronic mercurialism

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THE PURPOSE of this paper is twofold: first, to propose that amyotrophic lateral sclerosis and progressive muscular atrophy are probably nosologically identical, the latter being a variant of the former, and, second, to suggest that the term amyotrophic lateral sclerosis should not be used to denote a disease entity but rather a syndrome of variable etiology. Material will be presented in this paper in an attempt to elucidate these concepts.

REVIEW OF THE LITERATURE

For many years, there has been controversy regarding the proper classification of motor neuron disease. The term "progressive muscular atrophy" is associated with the names of Aran[1] and Duchenne.[2] Charcot[3] distinguished two varieties of this condition. Progressive muscular atrophy of the type of Aran and Duchenne was characterized only by lower motor neuron lesions. In the other, there were associated symptoms and signs of pyramidal tract involvement; this he called amyotrophic lateral sclerosis. The literature contains many reports in which amyotrophic lateral sclerosis and progressive muscular atrophy are regarded as nosologically identical. Wilson[4] mentions, for instance, that muscle wasting may be so profound as to mask coincidental pyramidal disease and that pyramidal lesions may be seen post mortem, even though hyperreflexia and other pyramidal tract signs had not been evident during life. Merritt,[5] Brain,[6] Adams, Denny-Brown, and Pearson,[7] and Nielsen[8] are of the opinion that progressive muscular atrophy is a variant of amyotrophic lateral sclerosis with lesions limited to the lower motor neurons. Others, such as Wechsler,[9] Alpers,[10] Müller,[11] and Magee,[12] however, express the belief that at least some cases of progressive muscular atrophy constitute a different clinical entity and carry a better prognosis because of limitation of the lesions to the lower motor neurons. This controversy over the appropriate classification can be expected in view of the lack of knowledge regarding the etiology of this disorder.

The conviction has gradually grown that amyotrophic lateral sclerosis is not one disease entity but a clinical syndrome of varying etiology. The literature contains several reports of this syndrome in which varied etiologic factors have been determined. One of the oldest concepts is that of abiotrophy. Cases of hereditary amyotrophic lateral sclerosis have been reported by Koerner[13] and Arnold, Edgren, and Palladino.[14] Kurland and Mulder[15] reviewed hereditary cases of progressive muscular atrophy and amyotrophic lateral sclerosis and found that from 1850 to 1955 at least 18 pedigrees had been reported involving 90 individuals. They added 6 pedigrees with 34 individuals.

Wechsler, Sapirstein, and Stein[16] analyzed 81 cases of amyotrophic lateral sclerosis and listed dietary, deficiency, inflammatory, vascular, and toxic processes as etiologic factors. The clinical symptom complex has been noted after gastrectomy,[17] polyarthritis,[18] and triorthocresyl poisoning.[19] Spinal cord tumors, syphilis, arachnoiditis, and epidemic encephalitis have been found to produce similar syndromes. Instances of progressive muscular atrophy have been described in patients with hyperinsulinism due to pancreatic adenoma;[20] in 4 cases,

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the atrophy was arrested after removal of the pancreatic tumor. Although there is no conclusive evidence that trauma plays any part in the etiology, the disease has been reported to follow or commence in an area that has undergone injury. It has also been considered as an atopic-stress disorder,[21] and some improvement has been reported to follow the use of adrenocortical extracts. Fullmer and associates[22] described a disorder of connective tissue in the dermis of about 60% of patients suffering from amyotrophic lateral sclerosis. This consists of [1] distinctive elastosis, [2] increase of mucopolysaccharide, [3] degeneration and elastosis of arrector pili muscles, [4] focal areas of regenerated connective tissue, and [5] alterations of collagen. Brown[23] reported 6 patients who had been chronically exposed to mercury in using a fungicide, Ceresan (phenylmercury acetate), while dusting oat seeds. All revealed the clinical findings of combined motor system involvement. A patient who presented the clinical picture of amyotrophic lateral sclerosis died in the hospital, and pathologic changes revealed at autopsy supported the diagnosis. The presence of large quantities of mercury in the urine established the etiology in this case.

STUDY OF MATERIAL

For many years, organic compounds of mercury have been used in the prevention of such seed-borne diseases of cereals as bunt of wheat, smut of barley, and leaf stripe of oats and barley. Since the use of organic compounds of mercury is a well-established principle of plant hygiene, ordinary seed wheat was treated with a fungicide called Granosan M (Dupont), 50 gm. of Granosan M to 100 kg. of wheat, before distribution by the Department of Agriculture of Iraq to thousands of poor farmers. The active ingredient of Granosan M is 7.7% ethyl mercury p-toluene sulfonanilide (total metallic mercury being 3.2%). The farmers were repeatedly told that the fungicide in the wheat contained a toxic ingredient and that such wheat was suitable only for planting and cultivation, not for consumption. In spite of frequent warnings, a number of them, all belonging to the very poor and illiterate classes, used such wheat in the preparation of bread and consumed their portion of seed wheat within a period of two to three months. It is a well-established custom in this country, especially among the poorer class, to eat homemade bread. Many cases of acute and chronic mercurialism were the result of consumption of such bread. We had the occasion to study 114 cases of chronic mercurialism with neurologic complications. The present report is limited to 11 patients belonging to this group, all of whom presented a clinical picture very akin to amyotrophic lateral sclerosis. Originally, this group consisted of 17 patients, but 6 patients were excluded because chemical studies failed to detect the presence of mercury. Mercury is excreted mainly through the urine, and this may continue for months after ingestion ceases. Spectrophotometric test for the detection of mercury in the urine, however, was not available in our hospital. Consequently, we had to rely on chemical studies performed on samples of hair and nails for detection of mercury in our patients. Such examination yielded positive results months after ingestion of mercury had ceased. It was also quite likely that, had spectrophotometric test for the detection of mercury in the urine been available, more positive results might have been obtained.

All 11 patients in our group were male farmers with ages ranging from 25 to 48 years. They admitted using their portion of treated seed wheat in the preparation of bread and had consumed it within a period of two to three months; 9 members of this group were also hospitalized for treatment of other symptoms of chronic mercurialism.

The symptoms of which the above 11 patients complained were sore mouth, metallic taste in the mouth, epigastric discomfort, vomiting, diarrhea, constipation, anorexia, polyuria, headache, fever, blurring of vision, insomnia, tremor of the hands, and psychic irritability. All had moderate to severe atrophy of the limb and trunk musculature with widespread fasciculations. Of the 6 patients with hyperreflexia, 4 had positive Babinski signs and the other 2 had an equivocal response. In 5 patients, there were no pyramidal tract signs. Except for the presence of slight atrophy of the tongue with fasciculations in 3 patients, no bulbar manifestations were noted. All modalities of sensation were normal. There were no sphincteric disturbances.

Physical examination was grossly within normal limits, except for the presence of gingivitis with a dark blue line at the gum margin in 7 patients and a generalized erythematous rash in 2 patients (see table).

SYMPTOMS AND SIGNS IN THE 11 CASES

Subjective	*Number of cases*
Sore mouth	7
Metallic taste in mouth	4
Anorexia	7
Epigastric discomfort	9
Vomiting	6
Diarrhea	7
Constipation	5
Polyuria	4
Headache	3
Fever	3
Insomnia	4
Blurring of vision	2
Tremor of hands	2
Psychic irritability	3
Objective	
Gingivitis with blue line at gum margin	7
Erythematous rash	2
Tremor of hands	2
Atrophy of tongue	3
Fasciculations	11
Atrophy of limb and trunk musculature	11
Motor weakness of limbs	11
Babinski sign	4
Babinski equivocal	2
Hyperreflexia	6
Hyporeflexia	5

Laboratory examinations. Chemical studies revealed the presence of mercury in samples of hair and nails obtained from all the patients in this group. There were no other significant findings except for albuminuria in 3 patients and microcytic anemia in 4.

Treatment and course in hospital. The period of hospitalization for these patients was approximately three months. Shortly after admission, a course of dimercaprol was administered to each patient in the following dosage schedule: 50 mg. every four hours for forty-eight hours, 50 mg. every six hours for another forty-eight hours, and 50 mg. every twelve hours for eight days. In addition to dimercaprol, these patients received several parenteral injections of vitamins B complex and B_{12}. Vitamin E was also given orally. No patient in this series responded to such treatment. Subsequent follow-up was possible with 4 patients for only a period of six months, and these are presented below.

Case 1. A 34-year-old farmer was admitted to the Neurological Unit with a complaint of loss of weight and weakness in the extremities. He had been well until four months before admission, when headache, anorexia, polyuria, abdominal colic, and diarrhea developed. He was free of these symptoms after three weeks. However, two weeks later, he complained of generalized aches, especially marked in the lower extremities. Shortly afterward, he experienced gradually increasing weakness in his extremities and also noted that he was losing weight.

The past medical history disclosed good health to the time of present illness. There was no history of neurologic disease in the family. The patient stated that six months before admission he, his wife, and 2 children had consumed homemade bread prepared from the wheat (containing Granosan M) given to them for the purpose of cultivation. The patient's wife and 2 children were also hospitalized for chronic mercurialism with neurologic complications.

General physical examination was normal. On neurologic examination, there was symmetric, diffuse wasting of the trunk and limb musculature. Motor power was moderately impaired in the extremities, especially in the lower limbs. Fasciculations were observed in the upper arms, trunk, and calves. Muscle tone and coordination were normal. The patient walked with some difficulty but had no sensory deficit. Abdominal reflexes were present. The deep reflexes were diminished on both sides, and there was no Babinski response.

Laboratory examinations. Spine and chest roentgenograms were normal. Blood count was as follows: red cells, 3,800,000 per cubic millimeter; hemoglobin, 75%; white cells, 6,500 per cubic millimeter; differential count, normal. Lumbar puncture showed the cerebrospinal fluid to be clear and under normal pressure. The cell count was normal, the protein was 30 mg. per 100 cc., and the globulin test was negative. Chlorides were 700 mg. per 100 cc., sugar was 90 mg. per 100 cc., and Wassermann reaction was negative. Fasting blood sugar was 100 mg. per 100 cc. Blood urea was 35 mg. per 100 cc. The urine showed +1 albumin; sugar was negative, and a moderate amount of pus cells was found. Mercury was detected in samples of hair and nails.

Treatment and course in hospital. The patient was hospitalized for a period of three months. He was given a course of dimercaprol, along with vitamin B complex and vitamins B_{12} and E. The

patient did not respond favorably to such treatment and continued to complain of aching in the extremities. It was also noted that he was having more difficulty with his gait. On reexamination six months later, it was noted that the wasting of the extremities was more marked and that he was having considerable difficulty in walking.

Case 2. A 46-year-old farmer noted swelling of the gums and a metallic taste and soreness in his mouth four and one-half months before his admission to the Neurological Unit. In the meantime, he complained of epigastric distress with occasional vomiting, diarrhea, and polyuria. He was almost free of these symptoms after a few weeks. However, shortly afterward, he experienced a sense of fatigue and heaviness in his lower limbs which was more obvious on walking for even short distances. This was soon followed by gradually increasing weakness, first in the left upper limb and shortly afterward in the right upper limb as well.

The patient's health before the onset of his present illness was good. Family history was devoid of neurologic disease. The patient was a bachelor but lived with 2 of his younger brothers. He admitted that six and one-half months before admission he and his 2 brothers had consumed bread prepared from wheat (containing Granosan M) given to them for the purpose of cultivation. They had consumed their share of wheat within a period of two months; 1 of his brothers was also a patient in our unit.

General physical examination was normal except for marked swelling of the gingivae, which also disclosed a bluish tinge. Neurologic examination showed a mild degree of atrophy of the tongue. Some fasciculations on the tongue were also noted. Motor power was moderately impaired in the limbs, especially in the left upper limb. There was a moderate degree of wasting of the limb and trunk musculature. Widespread fasciculations were noted in the shoulder girdles, chest, and thighs. The muscle tone, coordination, and gait were normal. He had no sensory deficit. Abdominal reflexes were present. The deep reflexes were present in the upper limbs and absent in the lower limbs. There was no Babinski sign.

Laboratory examinations. Spine and chest roentgenograms were negative. Blood count was as follows: red cells, 4,200,000 per cubic millimeter; hemoglobin, 85%; white cells, 8,000 per cubic millimeter; differential count, normal. Blood Wassermann reaction was negative. Lumbar puncture showed the cerebrospinal fluid to be clear and under normal pressure; the cell count was normal. Protein was 35 mg. per 100 cc., globulin test was negative, chlorides were 720 mg. per 100 cc., sugar was 90 mg. per 100 cc., and Wassermann reaction was negative. Fasting blood sugar was 80 mg. per 100 cc. Blood urea was 30 mg. per 100 cc. Urine was normal. Mercury was detected in samples of hair and nails.

Treatment and course in hospital. The patient received the usual treatment. There was neither any improvement nor further deterioration in his neurologic status after nine weeks of hospitalization. Reexamination after six months revealed more wasting in the limb musculature and more difficulty with his hands and gait.

Case 3. A 27-year-old farmer on admission complained of weakness of the extremities, tremor of both hands, and difficulty with speech of three months' duration. About four months before his present admission, he was hospitalized elsewhere for a very severe gastroenteritis which cleared within a period of two weeks. Shortly afterward, he experienced gradually increasing weakness of his extremities with severe generalized aches all over the body. Later, he noted tremor of his hands and also some difficulty with his speech.

The past and family histories did not disclose anything of pathologic significance. The patient admitted that, six months previously, he, his wife, and his 3 younger sisters had consumed homemade bread prepared from the wheat which contained the fungicide. In addition to the patient, 2 of his sisters were also hospitalized for chronic mercurialism accompanied by neurologic complications.

General physical examination was normal. There was a moderate degree of wasting in the limb and trunk musculature. Motor power was impaired in the limbs, especially in the right upper limb. Widespread fasciculations were noted on the trunk, shoulder girdles, thighs, and calves. Coordination was intact. Muscle tone was normal in the upper limbs. There was a moderate degree of hypertonicity in the lower limbs, and the patient's gait was slightly spastic. All modalities of sensation were intact. Abdominal reflexes were absent. The deep reflexes were normal in the upper limbs but exaggerated in the lower ones. Babinski sign was present on both sides.

Laboratory examinations. Spine and chest roentgenograms were normal. Blood count was as follows: red cells, 4,250,000 per cubic millimeter; hemoglobin, 80%; white cells, 7,500 per cubic millimeter; differential count, normal. Blood Wassermann reaction was negative. Lumbar puncture showed cerebrospinal fluid to be clear and under normal pressure; the cell count was normal. Protein was 40 mg. per 100 cc., globulin test was negative, chlorides were 720 mg. per 100 cc., and sugar was 80 mg. per 100 cc. Blood urea was 40 mg. per 100 cc. Urine was normal. Mercury was detected in samples of hair and nails.

Treatment and course in hospital. The patient was hospitalized for a period of three months. He was given the usual treatment but continued to complain of weakness in the extremities and often was quite irritable. Reexamination after six months revealed more wasting in the trunk and limb musculature; otherwise, no significant changes were noted.

Case 4. A 25-year-old farmer was in excellent health before his present illness. The family history was devoid of neurologic disease. About three months before hospitalization, he was ill for several days with anorexia, epigastric distress, occasional vomiting, and bouts of severe diarrhea. Shortly afterward, he experienced increasing weakness of the extremities and also noted loss of weight. He admitted that he had consumed homemade bread prepared from the wheat containing the fungicide. The patient's wife and an older brother were hospitalized for chronic mercurialism with nervous system involvement.

Physical examination was normal except for swollen and reddened gums with a dark blue line at the gum margins. Neurologic examination revealed moderately impaired motor power in the extremities, especially in the upper limbs. A moderate degree of wasting was found in the trunk and limb musculature. Fasciculations were noted on the trunk and shoulder girdles. The muscle tone, coordination, and gait were normal. He had no sensory deficit. Abdominal reflexes were present. The deep reflexes were present in the upper limbs but exaggerated in the lower ones. Plantar response was extensor on the right side but equivocal on the left.

Laboratory examinations. Spine and chest roentgenograms were normal. Blood count was as follows: red cells, 3,500,000 per cubic millimeter; hemoglobin, 75%; white cells, 7,000 per cubic millimeter; differential count, normal. Blood Wassermann reaction was negative. Lumbar puncture showed the cerebrospinal fluid to be clear and under normal pressure; the cell count was normal. Protein was 35 mg. per 100 cc., globulin test was negative, chlorides were 700 mg. per 100 cc., sugar was 100 mg. per 100 cc., and Wassermann reaction was negative. Fasting blood sugar was 90 mg. per 100 cc. Blood urea was 40 mg. per 100 cc. Urine was normal. Mercury was detected in samples of hair and nails.

Treatment and course in hospital. The patient's period of hospitalization was two months. He was given the usual treatment. Although there was no improvement in his condition, no further deterioration was noticeable. Neurologic examination on discharge was essentially the same as on admission. However, reexamination six months later revealed more wasting and weakness in the extremities. The gait was spastic, and a Babinski sign was present on both sides. Ankle clonus was found on the right side.

SUMMARY AND CONCLUSIONS

In this paper, 11 cases of chronic mercurialism with a neurologic picture akin to amyotrophic lateral sclerosis are reported. All these patients consumed bread prepared from wheat treated with a seed fungicide called Granosan M (Dupont). The active ingredient is 7.7% ethyl mercury p-toluene sulfonanilide. The period of consumption was about two to three months.

The physical examination was essentially normal, except for the presence of gingival swelling and a blue line at the gum margins in 7 patients and an erythematous rash in 2.

Neurologic examination disclosed motor weakness of the extremities and wasting of the limb and trunk musculature, with widespread fasciculations in the atrophic areas in all the patients. In this group, 6 patients had hyperreflexia, and there was a definite Babinski sign in 4 and an equivocal sign in 2. The remaining 5 patients had no pathologic pyramidal signs.

The underlying etiology was chronic mercurialism in all the patients. This was confirmed by detection of mercury in samples of hair and nails.

Because of the presence of pathologic pyramidal signs, 6 of the cases in this group would have been diagnosed as amyotrophic lateral sclerosis. The remaining 5 would have been labeled progressive muscular atrophy because of limitation of the lesions to the lower motor neurons.

We may conclude:

1] Since the same causative factor was operative in all these cases, it would appear that amyotrophic lateral sclerosis and progressive muscular atrophy are probably nosologically identical.

2] Amyotrophic lateral sclerosis should not be considered a disease entity but rather a syndrome of variable etiology.

3] Chronic mercurialism is a possible etiologic factor in amyotrophic lateral sclerosis.

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Spinal leptomeningeal ("pial") lipoma

A case report

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THE OCCURRENCE of lipomas in the spinal epidural space, where adipose tissue is found normally, is to be expected. The same may be said regarding the inclusion of fat in the tissue mass encountered in spinal dysraphism. However, the occurrence of tumor consisting of mature fat cells within the confines of the spinal leptomeninges in the absence of spina bifida is noteworthy. Although rare, cases of lipoma in this location have been reported by a number of authors.[1–7] The reports of Ehni and Love[1] and Caram, Scarcella, and Carton,[7] include excellent reviews of the previously reported cases. The latter were able to gather reports of 52 cases, including 2 of their own.

CASE REPORT

A 7-month-old Negro boy was admitted to the Medical College Hospital on February 5, 1959, with progressive paralysis of the upper limbs.

The patient was a twin with reported birth weight of 6 lb. Both twins were said to have been normal at birth and developed normally, although both remained underweight. The twin of this patient died unexpectedly during sleep at the age of 5 months. No information as to the cause of death is available.

The patient developed a respiratory infection about January 5, 1959. This illness apparently responded to antibiotics. Five days later, flaccid paralysis of the right upper limb was noted, followed by similar paralysis of the left upper limb a week later. He was transferred to this hospital thirteen days after the onset of paralysis.

On examination at the time of admission, the patient was alert and had a normal cry and shallow, gasping respirations. Weight was 11 lb. 9 oz.; length, 56.5 cm.; temperature, 102°; pulse, 150; respirations, 32 per minute. There was kyphosis of the thoracic spine. The skin overlying the area of kyphosis and to the left of the spine was erythematous and edematous, giving the appearance of chronic cellulitis. The cranial nerves were intact. Eyes, ears, nose, and oropharynx were normal. The neck was supple. Flaccid paralysis of both upper extremities and the shoulder and neck muscles and spastic paralysis of both lower extremities were noted. Tendon reflexes were absent in the upper extremities but were hyperactive in the lower extremities. Sustained ankle clonus was noted bilaterally. The plantar response was extensor bilaterally. There was no response to pinprick over the limbs or trunk below the neck.

The hemoglobin was 9.5 gm.; red blood cell count, 4,560,000; white blood cell count, 9,800 with 59% polymorphonuclear cells, 39% lymphocytes, 1% monocytes, and 1% eosinophiles. A sickle cell preparation was negative. The blood serology (Kolmer and Kline) was negative. The urine was normal. On lumbar puncture, 3 cc. of xanthochromic cerebrospinal fluid was obtained under an opening pressure of 80 mm. The fluid contained no cells and 171 mg. per cent total protein. Roentgenograms of the skull and long bones were normal. Anteroposterior and lateral views of the spine showed widening of the cervical canal but no erosion. The chest roentgenogram was normal except for bilateral elevation of the diaphragm.

On the day after admission, a myelogram was attempted but no cerebrospinal fluid could be obtained at the lumbar level. A cisternal puncture was performed, and 2 cc. of Panto-

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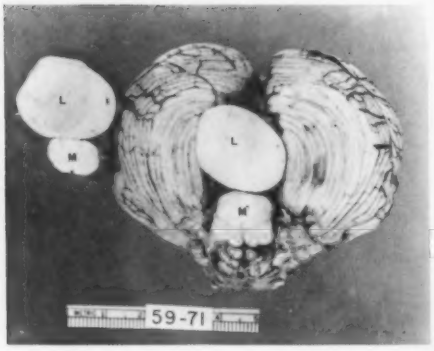

Fig. 1. Inferior view of cerebellum and brain stem, showing relation of lipoma (L) to medulla oblongata (M) and cerebellum

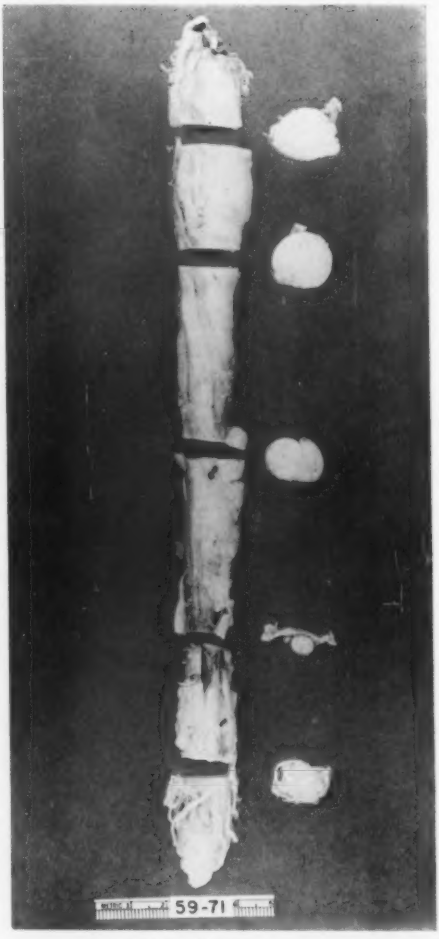

Fig. 2. Spinal cord, posterior view. Notice relatively normal portion of lumbar region, shown in cross section with dura attached.

paque was introduced into the cisterna magna. Roentgenograms in the upright position revealed a complete block to the flow of the contrast media at the foramen magnum.

A cervical laminectomy was performed, revealing what was thought to be markedly thickened dura overlying the upper cervical spinal cord posteriorly and obliterating the subdural and subarachnoid spaces. No flow of spinal fluid through the foramen magnum was obtained. A biopsy of the tissue overlying the spinal cord consisted of dense fibrous and collagenous tissue histologically.

After operation, there was progressive increase in spasticity and rigidity in the lower extremities. Tachycardia persisted, and respirations remained shallow and rapid. The child remained alert. Accumulation of secretions in the upper respiratory tract presented an increasing problem. The child died on the eighteenth postoperative day, thirty-one days after the onset of paralysis.

Postmortem findings. Autopsy was performed twelve hours after death. The body measured 64 cm. in length and the head 41 cm. in the frontooccipital circumference. There was edema of the skin surrounding a high cervical operative scar. The body otherwise was normal on external inspection. The lungs had scattered areas of bronchopneumonia and atelectasis. The posterior branches of the bronchi were occluded by thick, brown mucus. The heart and great vessels, spleen, pancreas, liver, intestinal tract, adrenals, and urinary tract were all normal.

The brain weighed 650 gm. The cerebral hemispheres and meninges were normal. In the posterior fossa, protruding through the foramen magnum and lying along the dorsal surface of the medulla oblongata, was a smooth, light-yellow, firm, rubbery mass extending up between the tonsils of the cere-

bellum, where it ended in a rounded knob (Fig. 1). Inferiorly, it continued through the foramen magnum and down the posterior aspect of the spinal canal to the cauda equina, obliterating the subarachnoid space and displacing the spinal cord anteriorly. A 2.5-cm. length of spinal cord in the lumbar region appeared normal, was not covered by the mass, and had a fluid-filled subarachnoid space (Fig. 2).

On cross section, the mass was homogeneous and had a greasy texture. In many sections, it was intimately adherent to the spinal cord so that identification of the cord margins was impossible. It was attached to the inner surface of the dura by fine fibrous strands in many places but did not penetrate or invade the dura, which stripped away easily.

Histologic examination of paraffin-imbedded sections stained with hematoxylin and eosin revealed that the mass consisted entirely of mature fat cells enclosed in a thin capsule of fibrous tissue which was continuous with a thickened pial membrane (Fig. 3). It was densely adherent to the posterior surface of the spinal cord, but, at every level, the tumor was separated from the spinal cord by its pial capsule (Fig. 4). In places, the thickened pial capsule was closely adherent to the dorsal surface of the cord, but nowhere were intramedullary fat cells found. In several cross sections, nerve roots were found passing posterolaterally through the tumor mass. The spinal cord was markedly flattened and distorted. The pia-arachnoid membrane extending laterally and anteriorly around the cord was perhaps slightly thickened but not otherwise of remarkable appearance. The tumor was confined to the dorsal and dorsolateral surface with relation to the spinal cord.

Fig. 3. Cross section at thoracic level of cord. Capsule of tumor continuous with pia-arachnoid, which is thickened adjacent to spinal cord. Segment of a nerve root passing through tumor is shown. Hematoxylin and eosin. × 15

DISCUSSION

Most of the previously reported cases of leptomeningeal lipoma have been less extensive than this case. However, at least 2 cases[5,6] have been reported previously in which the tumor extended the entire length of the spinal cord.

In spite of its relationship to the spinal meninges, there seems no justification for regarding this tumor as a meningioma. It was not associated with spinal dysraphism and was confined to the subarachnoid space throughout its extent. Except for kyphoscoliosis, there were no associated congenital malformations such as have been reported in other cases.[5,6]

The rapid clinical course is an interesting feature of this case, suggesting either rapid growth of the tumor or increase in its size due to edema. Lipomas generally are not prone to rapid growth. Theories as to the origin of lipomas in this location have been discussed by Ehni and Love[1] and summarized

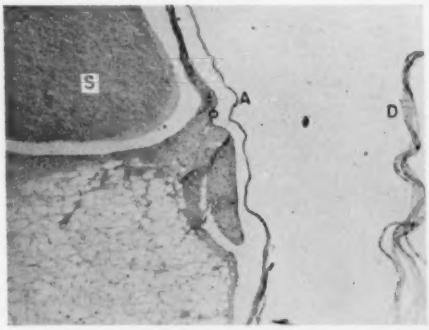

Fig. 4. Area of spinal cord (S), lipoma, and capsule showing relation of dura (D), arachnoid (A), and pia (P), which is thickened. Hematoxylin and eosin. × 60

by Viñas and Poppen.[2] One hypothesis includes the concept of a deficiency in the pial tissue of some unknown factor normally present which holds in abeyance the development of fat from persisting mesenchymal cells of pial capillaries. It is conceivable that extreme deficiency of such a hypothetic factor would permit not only the occurrence of this tumor in this location but also its unusually rapid and extensive growth.

SUMMARY

A case of leptomeningeal ("pial") lipoma in a 7-month-old Negro boy is presented. The tumor was confined to the subarachnoid space along the dorsal aspect of the spinal cord and lower brain stem, extending from the level of the rostral end of the medulla oblongata to the cauda equina, a 2.5-cm. section in the lumbar segments of the cord being spared. The clinical manifestation was that of paralysis beginning in the left upper limb and progressing to quadriplegia, with death due to respiratory paralysis thirty-one days after onset of symptoms.

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Mental Retardation. Proceedings of the First International Medical Conference

edited by Peter W. Bowman and Hans V. Mautner, 530 pp., ill., Grune & Stratton, Inc., New York City, 1960. $12.50.

The First International Medical Conference on Mental Retardation was held in Portland, Maine, in 1959. One realized on review of the papers the important advances that have been made in understanding the causes of mental retardation. From the anatomic studies, through the exciting work in enzyme chemistry and chromosomes, to the fine papers on childhood schizophrenia and behavior disorders, one is impressed with the fine quality of the work and the advances that are being made. The program committee and the editors are to be complimented on the fine selection of essayists and the manner in which the material is presented. This volume is highly recommended for those working in the field of mental retardation.

J.P.R.

Histonomy of the Cerebral Cortex

by S. T. Bok, 434 pp., Elsevier Publishing Company, Amsterdam, London, New York, and Princeton, 1959. $14.50.

This treatise introduces a new approach to the study of the cerebral cortex. The histonomic method of investigation is well defined by the author: "measuring numerous morphological details by means of the microscope, deducing laws from the data obtained and building biological theories on the basis of these laws." He points out that, by such measuring methods, the most important results have been achieved in physics and astronomy and that unexpected insight can be gained into the finer structure of living nature, notwithstanding its marked irregularities.

Within the limits of this review, some of the studies and conclusions may be summarized.

In the sulci and gyri, the cerebral cortex is curved; when a given pattern is to be arranged to conform to a given curve, the original size, shape, and relative arrangement of its elements cannot all at the same time be maintained. While the histologic pattern changes, function is unaffected. The naming of subareas of the original Brodmann fields is unnecessary since these coincide with parts where the cortex shows a curvature.

The cortical neurons, varying largely in size, obey exact quantitative rules. The surface of the cell body and the average length of its dendrites are proportional to the volume of their nucleus.

A simple but hitherto undescribed type of variation in the size of the neurons results in the arrangement of the cortex into layers and architectural fields.

In the various mammalian species, the average size of the dendrite trees and consequently the height of the cortex and its nerve cell density are quantitatively related in a simple way to the size of the animal body.

The surface extension of the cortex, and thus the total number of its nerve cells, changes with both the body size and the degree of biologic development (according to the Linnaeus system of classification). On the basis of these quantitative relations, a theory is developed according to which the

nervous system plays the primary role in the genesis of higher animal species.

Everywhere in the animal and human cortex, the nerve fiber network is found to have equal density and to present globular vacuoles situated at a constant distance from each other, each containing a mitochondrium. Assuming that the morphologic relation of the vacuoles to the nerve fibers is analagous to the relation of the electronic sensitive units to the signaling wires in an artificial memory apparatus, the hypothesis is that these interfibral vacuoles are the special organs of memory.

This book is on excursion into physical neurology. Based on numerous planned measurements, it opens vast vistas of speculation. As one may surmise, calculations are set down in detail, so that the reader with a mathematical turn of mind will be especially interested.

A.R.V.

Electrical Studies on the Unanesthetized Brain

by Estelle R. Ramey and Desmond S. O'Doherty, 423 pp., ill., Paul B. Hoeber Inc., New York City, 1960. $6.00.

This book arose from a symposium made up of 20 chapters drawn from the disciplines of psychiatry, psychology, physiology, neurophysiology, neurosurgery, and neurology by 49 participants. The participants have in common their interest in the varied aspects of electrical activity of the unanesthetized brain of experimental animals and man.

A few chapters had particular interest for these reviewers. Among them were Nauta's description of the pathways of the limbic system, Patton's report of fatal lung hemorrhage and edema associated with hypothalamic lesions, Delgado and Hamlin's demonstration of the patterns of spontaneous and evoked electrical seizures, and Baldwin's observations upon the effect of direct stimulation of the mesial temporal region. Subject matter varied from the reasons for using stainless steel probes instead of copper, silver, or other ones (histologic evidence for local absorption of the metals) to psychologic studies. In the latter, difficulties are experienced in defining behavior and in stating how complex acts are influenced by the environment. The resultant overloading lends weakness to this portion of the book, not because of any failure on the author's part but because of difficulties inherent in the reporting job undertaken.

An excellent summation and constructive critique is provided by Rioch, who points up the special difficulties in the symposium and outlines the problems that are dealt with. He noted the ignorance that exists concerning the source and significance of spontaneous electroencephalographic activity and the unreliability of any nosologic classification based upon diagnostic evidence. Also stressed was the difficulty that exists in defining the functions of the special centers of the brain.

In summary, the work represents a brave effort to correlate the many aspects of electrical studies carried out in the depths of the brain, but the investigators are plagued by the multiplicity of structural variations in the position of centers and the overlaps between them which exist in the basal parts. This makes it especially difficult to establish precisely the sources of the records interpreted. The work is valuable in emphasizing that far more of the road to understanding lies in front of than behind us and in indicating the tireless energy which is needed even to establish the foundations leading to profitable study.

B.H. & J.L.O.

Parkinson's Disease—
Its Meaning and Management

by Louis J. Doshay, 124 pp., J. B. Lippincott Co., Philadelphia, 1960. $1.45.

This small paperback book is intended for popular use by the patient and by the family of the patient with Parkinson's disease. The book undertakes to answer the specific questions of lay persons concerning the disease. Emphasis is placed on the favorable aspects of the disorder. Medical and physical treatments are discussed in good detail, and surgical treatment is given reasonable space. Of particular note is the chapter devoted to what the patient can do for himself. The book reflects the long and detailed experience of the author with the science and art of treating patients with parkinsonism. Although written for lay consumption, many aspects of the book are of value to the physician.

J.R.B.

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*Ayd, Frank J., Jr.: Drug-induced Extrapyramidal Reactions: Their Clinical Manifestations and Treatment with Akineton. Psychosomatics 1:143 (May-June) 1960.

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Patients already receiving other anticonvulsants—Adults and Children (over 8 years): 0.25 Gm. daily, and gradually increased while the dosage of the other drug(s) is gradually decreased. Continued until satisfactory dosage level is achieved for combination, or until other medication is completely withdrawn. *Children under 8 years:* Initially one-half the adult dose, or 0.125 Gm. daily. Gradual increases and decreases as described in adult regimen. (Where a smaller starting dose is required, use 50 mg. tablet.)

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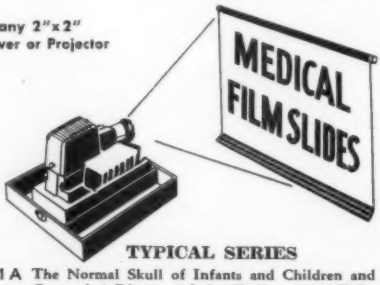

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

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JULY 1961

ANA Meets in Atlantic City The American Neurological Association held its eighty-sixth annual meeting at the Claridge Hotel, Atlantic City, June 12 through 14, 1961. The ANA scientific program opened on Monday morning, June 12, with the presidential address of Harold G. Wolff and was followed by 42 free papers and their discussions -- the sessions terminating on Wednesday noon, June 14; 29 papers were read by title. In addition, there were 6 scientific exhibits and/or demonstrations and 4 technical exhibits (Baltimore Instrument, Grass Instrument, Medcraft Electronics, Robert Brunner, and Teca Corporation). The annual dinner for ANA members and guests was held in Trimble Hall at 7 p.m., Tuesday, June 13, with a program of entertainment and dancing....The ANA sessions were preceded by the meetings of the American Electroencephalographic Society, June 9 through 11, the Society of Biological Psychiatry, June 9 through 11, and the American Association of Neuropathologists, June 10 through 11. The electroencephalographers and biologic psychiatrists met at the Claridge Hotel while the neuropathologists met at the Shelbourne Hotel. On Monday evening, June 12, the ANA conducted a joint symposium with the American Association of Neuropathologists. The topic was "Properties of Membranes and Diseases of the Nervous System," which was chaired by A. Earl Walker.

O'Leary Becomes ANA President At the end of the third ANA Executive Session June 14, James L. O'Leary assumed the responsibilities of the ANA presidency. Other officers elected were Charles D. Airing, President-Elect; Francis B. McNaughton, First Vice-President; and Robert S. Schwab, Second Vice-President. Melvin D. Yahr, Editor of the ANA Transactions, and Clarke Millikan continue as Secretary-Treasurer and Assistant Secretary, respectively. Harold G. Wolff was elected to the Council for five years and Fred Plum for two years. Charles Rupp was appointed as representative to the American Board of Psychiatry and Neurology and Derek Denny-Brown as representative to the National Research Council. Russell N. DeJong was appointed delegate and Gilbert H. Glaser alternate delegate to the World Federation of Neurology....During the 1961 ANA sessions, 11 candidates were elected to active membership and 7 to associate membership. The new active members are P. R. Dodge, N. P. Goldstein, Albert Heyman, Edward Richardson, Harold Koenig, F. H. McDowell, Huntington Porter, G. M. Shy, James Stephens, T. E. Twitchell,

and Charles Van Buskirk. The new associate members are E. C. Alvord, Jr., P. J. Harmon, E. H. Lambert, V. B. Mountcastle, D. P. Purpura, L. F. Chapman, and M. B. Carpenter....The ANA will hold its eighty-seventh annual meeting June 17 through 20, 1962, at the Claridge Hotel, Atlantic City.

Western Institute To Hold Conference The Western Institute on Epilepsy will conduct its thirteenth annual conference at the Granada Hotel and Inn in San Antonio, October 11 through 14, 1961. The scientific presentations will focus primarily on the clinical, biochemical, neurophysiologic, psychologic, and electroencephalographic aspects of epilepsy. President and Secretary-Treasurer, respectively, of the Institute are John L. Otto and Frank D. Risch, 3097 Manning Avenue, Los Angeles 64.

Los Angeles Group Elects New Officers The Los Angeles Society of Neurology and Psychiatry, at its annual meeting, January 18, 1961, elected Nicholas A. Bercel President and Robert P. Sedgwick President-Elect. Robert N. Baker continues as Secretary-Treasurer. The present Councilors of the Society are John D. French, Augustus S. Rose, G. Creswell Burns, Carlo P. DeAntonio, and John R. Peters....On February 17 and 18, 1961, the Los Angeles Society conducted a symposium on recent contributions of basic research to paraplegia.

Here and There Wilder Penfield delivered the twenty-seventh annual Hughlings Jackson lecture of the Montreal Neurological Institute, June 2, 1961. His subject was "The Brain's Record of Experience, Auditory and Visual." Dr. Penfield also gave, in 1935, the inaugural lecture of this series with an address on epilepsy and surgical therapy.... NINDB Director Richard L. Masland chaired the neurology scientific session of the fiftieth anniversary of the Lynchburg Training School and Hospital in Colony, Virginia, on May 17, 1961. The academic lecture at this scientific session was given by C. E. Benda, on the "Relationship of Cerebral Palsy to Prenatal and Paranatal Disorders."...
The Pergamon Press will publish a new trimonthly periodical, JOURNAL OF NEUROPHARMACOLOGY, which the publishers will supplement with an annual review, PROGRESS IN NEUROPHARMACOLOGY. The purpose of the new publication is to bring together original work and up-to-date reviews in neuropharmacology that will serve both the neuropharmacologist in the laboratory and the clinical neurologist.
...Four WFN Problem Commissions will conduct special symposia in conjunction with the Seventh International Neurological Congress in Rome September 10 through 16, 1961: Geographic Isolates in Neurologic Research (Commission of Biometry and Genetics); Leucodystrophy and the Lipids, the Lipoproteins and Their Metabolism (Commission on Neurochemistry); Genetics of Muscular Disease (Commission of Neurogenetics) which is being conducted in coopera-

tion with the Third International Congress of Human Genetics and the Muscular Dystrophy Associations of America; and The History of Italian Neurological Science (Commission of the History of Neurology)....A two-day symposium on the problem of cerebral tumors, organized by K. J. Zülch and sponsored by the WFN, will be held in Cologne August 30 through September 1, 1961.... Knude Krabbe, distinguished long-time leader of Danish neurology, died on May 7, 1961. For several years, he had been afflicted with paralysis agitans. Professor Krabbe's death is a keenly felt loss to both Danish and world neurology.

International Conference Focuses on Cerebral Dominance

On April 24 and 25, a group of international authorities convened at the Johns Hopkins School of Medicine for a two-day conference on some of the unsolved problems of cerebral dominance. The conference was sponsored by the National Institute of Neurological Diseases and Blindness and the Johns Hopkins University School of Medicine. The discussions were centered on anatomic symmetries of the cerebral hemispheres; mechanisms for functional hemispheric integrations in lower animals; functional differences between the hemispheres of the human brain; and the problem of defining a valid concept of dominance. Among the participants were Macdonald Critchley and George Ettlinger (London); Richard Jung (Freiburg); H. Hécaen (Paris); Hans-Lucas Teuber; James L. O'Leary; and Harold G. Wolff.

AAN Applications for Senior Membership

Richard L. Masland, Chairman of the AAN Membership Committee, wishes to call to the attention of AAN members Section 8 of Article III of the AAN Constitution, which reads as follows: "Senior members shall be elected from Active members or Fellows who have retired from active participation in neurology and the affairs of the Academy." All AAN members who have reached retirement status are requested to forward applications for senior membership to the AAN Executive Secretary, Mr. Thomas Swedien, 4307 East 50th Street, Minneapolis 17.

Electroencephalographers Meet in Atlantic City

The American Electroencephalographic Society held its fifteenth annual meeting at the Hotel Claridge, Atlantic City, June 9 through 11. Two symposia were highlighted on the scientific program: the medicolegal electroencephalogram, Isadore S. Zfass, Chairman, and the physiologic basis of memory, Frank Morrell, Chairman.

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References: 1. Finkel, M. J.: M. Times 86:1391, 1958. 2. Doshay, L. J., and Boshes, L.: Postgrad. Med. 27:602, 1960. 3. A. M. A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, J. B. Lippincott Company, 1960, p. 264. COGENTIN is a trademark of Merck & Co., Inc.

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(1) Carter, S.: *M. Clin. North America* 37:315, 1953.
(2) Maltby, G. L.: *J. Maine M. A.* 48:257, 1957.
(3) Buchthal, F.; Svensmark, O., & Schiller, P. J.: *Arch. Neurol.* 2:624, 1960.

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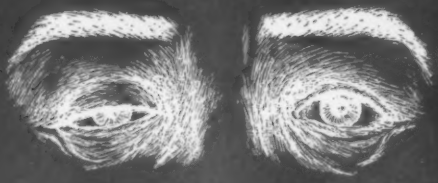

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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

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